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Proposed Re-evaluation Decision PRVD2014-03

Metiram

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Table of Contents

Overview ... 1
  Proposed Re-evaluation Decision for Metiram ... 1
  What Does Health Canada Consider When Making a Re-evaluation Decision? ... 2
  What is Metiram? ... 3
  Health Considerations ... 3
  Environmental Considerations ... 6
  Value Considerations ... 7
  Proposed Measures to Minimize Risk ... 8
  What Additional Scientific Information Is Identified? ... 9
  Next Steps ... 9
Science Evaluation ... 11
1.0 Introduction ... 11
2.0 The Technical Grade Active Ingredient, Its Properties and Uses ... 11
  2.1 Identity of the Technical Grade Active Ingredient ... 11
  2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient ... 12
  2.3 Description of Registered Metiram Uses ... 12
3.0 Impact on Human and Animal Health ... 13
  3.1 Toxicological Summary ... 13
    3.1.1 PCPA Hazard Characterization ... 17
  3.2 Occupational and Non-Occupational Risk Assessment ... 18
    3.2.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment ... 19
    3.2.2 Occupational Exposure and Risk Assessment ... 20
  3.3 Dietary Risk Assessment ... 24
    3.3.1 Determination of Acute Reference Dose ... 25
    3.3.2 Acute Dietary Exposure and Risk Assessment ... 26
    3.3.3 Determination of Acceptable Daily Intake ... 27
    3.3.4 Chronic Dietary Exposure and Risk Assessment ... 27
    3.3.5 Cancer Potency Factor q_1^* ... 28
    3.3.6 Cancer Dietary Exposure and Risk Assessment ... 28
  3.4 Exposure from Drinking Water ... 29
    3.4.1 Concentrations in Drinking Water ... 29
    3.4.2 Drinking Water Exposure and Risk Assessment ... 29
  3.5 Aggregate Risk Assessment ... 29
  3.6 Cumulative exposure and risk assessment ... 30
  3.7 Incident Reports ... 30
4.0 Impact on the Environment ... 31
  4.1 Fate and Behaviour in the Environment ... 31
  4.2 Environmental Risk Characterization ... 32
    4.2.1 Risks to Terrestrial Organisms ... 33
    4.2.2 Risks to Aquatic Organisms ... 36
    4.2.3 Conclusion on Environmental Risks ... 38
    4.2.4 Incident Reports, or Special Use Pattern ... 39

5.0 Value ... 39
  5.1 Commercial Class Uses for Which Information on the Value of Metiram is Sought ... 39
  5.2 Value of Metiram ... 39
    5.2.1 Uses ... 39
    5.2.2 Apple Scab ... 40
    5.2.3 Early and late blights on potatoes and tomatoes ... 40
    5.2.4 Asparagus rust ... 41
    5.2.5 Resistance Management ... 41
6.0 Pest Control Product Policy Considerations ... 42
  6.1 Toxic Substances Management Policy Considerations ... 42
  6.2 Formulants and Contaminants of Health or Environmental Concern ... 42
7.0 Summary ... 43
  7.1 Human Health and Safety ... 43
    7.1.1 Occupational Risk ... 43
    7.1.2 Dietary Risk from Food ... 44
    7.1.3 Aggregate Risk from Food and Water ... 44
    7.1.4 Cumulative Risk ... 44
  7.2 Environmental Risk ... 45
  7.3 Value ... 45
8.0 Proposed Regulatory Decision ... 46
  8.1 Proposed Regulatory Actions ... 46
    8.1.1 Proposed Regulatory Action Related to Human Health ... 46
    8.1.2 Proposed Regulatory Action Related to Environment ... 50
  8.2 Additional Identified Data ... 52
    8.2.1 Data Related to Toxicology ... 52
    8.2.3 Data Related to Occupational Exposure ... 53
    8.2.4 Data Related to Food Residue Chemistry ... 53
    8.2.5 Data Related to Environment ... 54
    8.2.6 Data Related to Value ... 54
List of Abbreviations ... 55
Appendix I Metiram Products Registered in Canada (Excluding Discontinued Products or Products with a Submission for Discontinuation) as of 31 October 2012 ... 59
Appendix II Commercial Class Uses of Metiram Registered in Canada, Excluding Uses of Discontinued Products or Products with a Submission for Discontinuation as of 31 October 2012 ... 61
Appendix III Uses of Metiram in Canada for Those Site-Pest Combinations of Commercial Class Products for which Risk Concerns Have Been Identified ... 63
Appendix IV Toxicity Profile and Endpoints for the Health Risk Assessment for Metiram and ETU ... 65
  Table 1 Toxicology Profile for Metiram from PMRA and foreign reviews ... 65
  Table 2 Toxicology Profile for ETU ... 73
  Table 3 Toxicology Endpoints for the Health Risk Assessment for Metiram ... 86
  Table 4 Toxicology Endpoints for the Health Risk Assessment for ETU ... 87

Appendix V Agricultural Mixer/Loader/Applicator and Post-Application Risk Assessment. 89
Table 1 Dermal and Inhalation MOEs for Short-to-Intermediate Term Mixing/Loading and Applying Metiram 89
Table 2 Dermal and Inhalation Short-to-Intermediate Term MOEs for ETU from Mixing/Loading and Applying Metiram 91
Table 3 ETU Cancer Exposure and Risk Estimates for Occupational Handlers 92
Table 4 Restricted Entry Interval for Commercial Post-Application Activities for Metiram 94
Table 5 ETU MOEs for Commercial Post-Application Activities for Metiram 94
Table 6 ETU Cancer Risk for Post-Application Workers 95
Appendix VI Dietary Exposure and Risk Estimates for Metiram 97
Table 1 Acute and Chronic Dietary Exposure and Risk Estimates for Metiram 97
Table 2 Acute and Chronic Dietary Exposure and Risk Estimates for ETU 97
Table 3 Cancer Dietary Exposure and Risk Estimates for ETU 98
Appendix VII Food Residue Chemistry Summary 99
Table 2 Summary of Analytical Methods 103
Table 3 Summary of Storage Stability for Metiram and ETU 105
Table 4 Metiram and ETU residues in plant commodities 107
Table 5 Metiram and ETU Processing Factors derived from field trials 112
Table 6 Metiram and ETU Commercial Processing Factors 113
Appendix VIII Supplemental Maximum Residue Limit Information - International Situation and Trade Implications 115
Table 1 Differences Between Canadian MRLs and Other Jurisdictions 115
Appendix IX Environmental Assessment 119
Table 1 Fate and Behaviour in the Environment 119
Table 2 Toxicity to Non-Target Species 124
Table 3 Screening Level Risk Assessment on Non-Target Terrestrial Species Other Than Birds And Mammals 131
Table 4 Screening Level Risk Assessment for Birds and Mammals Using Maximum Kenaga Values 132
Table 5 Screening Level Risk Assessment For Aquatic Non-Target Organisms 133
Table 6 Refined Reproduction Risk Assessment for Birds and Mammals Using Mean Kenaga Values 133
Table 7 Temporal Chronic Risk as a Result of Metiram on Avian and Mammalian Food Items Based on Kenaga Maximum and Mean Residues 137
Table 8 Refined Risk Assessment For Non-Target Aquatic Organisms Using Percent Drift Deposition for Applications 137
Table 9 Comparison of Risk Quotients from Refined Risk Assessment Using the Current Registered Application RATEs and the USEPA Recommended Application Rates 138
Table 10 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria 139

Appendix X Monitoring Data 141
Table 1 Summary of Available Monitoring Studies and Data 141
Table 2 Level 1 and Level 2 estimated environmental concentrations of ETU in potential drinking water sources 142
References 143

Overview

Proposed Re-evaluation Decision for Metiram

After a re-evaluation of the fungicide metiram, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing phase-out of metiram uses in Canada.

An evaluation of available scientific information found that under the current conditions of use, the human health and environmental risks estimated for metiram do not meet current standards. The assessment presented in this document identified risks to the general population through dietary (food and drinking water) exposure, risks to workers during re-entry activities as well as risks to the environment. At this time, these assessments support a phase-out of metiram and all associated uses – in other words, on apple, asparagus, celery, root and tuber vegetables (such as carrot, sugar beet and potato), grapes and tomato. Additional risk-reduction measures are proposed during the phase-out of metiram.

A consultation with the registrant, during the re-evaluation process, resulted in discontinuation of the use of a metiram dust product on foliage of potato, tomato, celery and grape, and the use of a metiram powder product on potato seed pieces for the control of Fusarium seed decay and seed-borne common scab. These two products are no longer supported by the technical registrant and their uses were not considered in the risk assessments. Further changes to the use pattern are needed to address the risk concerns identified with uses currently registered in Canada.

The PMRA is soliciting from the public and all interested parties, information that may be used to refine the occupational, dietary, and environmental risk assessments and/or mitigate risks. During the consultation period, the registrant has the opportunity to provide additional data and propose changes to the use pattern that could be used to address the risk concerns. If additional scientific data and/or changes to the use pattern are not adequate to address the risk concerns, uses of metiram will be phased-out.

Health Canada's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information.

This proposal affects all end-use products containing metiram registered in Canada. The PMRA will consider the information received during the comment period and will make a final decision on the phase-out of metiram after that assessment is complete.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for metiram and presents the reasons for the proposed re-evaluation decision.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of metiram.

The PMRA will accept written comments and information up to 45 days from the date of publication of this document. Please forward all comments on this proposal to Publications (see contact information on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[2] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at www.healthcanada.gc.ca/pmra.

Before making a re-evaluation decision on metiram, the PMRA will consider all comments received from the public in response to this consultation document.[4] The PMRA will then publish a Re-evaluation Decision document[5] on metiram, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

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[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[2] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[3] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

[4] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[5] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

For more details on the information presented in this overview, please refer to the Science Evaluation of this consultation document.

What is Metiram?

Metiram is a broad spectrum, preventive contact fungicide belonging to the ethylenebis(dithiocarbamate) (EBDC) group. It works via multi-site contact activity and falls under the Resistance Management Mode of Action group M3. Metiram is used to control a broad range of fungal pathogens on a number of terrestrial food crops including:

- apple,
- asparagus,
- celery, root and tuber vegetables (carrot, sugar beet and potato including potato seed treatment),
- grapes, and
- tomato.

Metiram is applied as a foliar fungicide using conventional ground and aerial (potato only) application equipment and as a potato seed treatment by growers, farm workers and professional applicators. There is no residential use of metiram registered in Canada.

Health Considerations

Can Approved Uses of Metiram Affect Human Health?

Risks of concern have been identified from dietary exposure to metiram and its metabolite ethylene thiourea, and from worker postapplication exposure to metiram.

Metiram is a broad spectrum fungicide of the EBDC group of fungicides (mancozeb, maneb, zineb and nabam) that also metabolizes in the body and the environment to the common degradate of the EBDC fungicides, ethylene thiourea (ETU).

Potential exposure to metiram may occur through the diet, when handling the product or by entering treated sites. Similarly, potential exposure to ETU may also occur through the diet, when handling the product or by entering treated sites where application of the EBDC group of fungicides has occurred. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers).

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed.

Metiram was of low acute oral toxicity to mice and rats, low dermal and inhalation toxicity to rats and non-irritating to rabbit eye and skin. Metiram was a skin sensitizer in guinea pigs.

ETU was of low-moderate acute oral toxicity to pregnant/non-pregnant mice, hamsters and rats. It was of low acute dermal and inhalation toxicity to rabbits and rats, respectively, and non-irritating to rabbit skin and eyes. ETU was a dermal sensitizer in guinea pigs.

For metiram the most sensitive endpoints were effects on the thyroid and nervous system. In pregnant rats, increased postimplantation loss was noted in the presence of toxicity to the mothers (body weight effects).

For ETU the most sensitive endpoints in laboratory animals were developmental, liver and thyroid effects. Based on supplemental reproduction toxicity studies, the thyroid was the primary target in adult rats and mice and the primary effect in pups was decreased survival. Developmental toxicity occurred via the oral and dermal routes of exposure, with rats being the most sensitive species. After dermal exposure on gestation days 12-13, all fetal rats had marked skeletal malformations, at non-maternally toxic doses. Although maternal thyroid toxicity is often associated with developmental effects, this potential thyroid-mediated mode of action was not applicable to developmental effects resulting from acute exposure, as ETU was a direct developmental toxin in the rat. In published studies, no developmental effects were noted in hamsters or guinea pigs. In mice, the only developmental effect observed was an increase in supernumerary ribs. Cats had malformations in their offspring at doses that were also toxic to mothers. Rats may have a differential sensitivity because of the way ETU is metabolized, compared to the mouse, rabbit, hamster, guinea pig and cat.

Cancer concerns exist for metiram based on ETU, a metabolite of metiram. ETU has been shown to cause thyroid cancer in both mice and rats, and liver cancer in female mice. The mutagenic test data on ETU yielded both positive and negative results. The weight of evidence indicates that metiram is not genotoxic.

The risk assessment compares the level of human exposure to the dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are of concern.

Chronic dietary risk from metiram and dietary cancer risks from ETU are of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake (ADI) is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Dietary exposure was estimated for metiram as well for the ETU metabolite. As metiram is not expected to occur in drinking water, the metiram assessment includes chronic and acute risk estimates from food consumption only, whereas the ETU assessment includes acute and chronic risk estimates from consumption of both food and water. In addition, a cancer risk assessment was conducted for ETU from exposure through food and drinking water.

Metiram dietary risk

The chronic exposure to metiram from food ranges from 8% to 128% of the ADI for different sub-populations, with the highest value for children aged 1 to 2 years old and is therefore of concern. Acute exposure to metiram from food is 88% of the ARfD (95th percentile) for females aged 13-49, and is not of concern.

Ethylene thiourea dietary risk

During the re-evaluation, it was determined that ETU is a residue of toxicological concern. As a result, toxicological endpoints were determined for this metabolite and separate acute, chronic and cancer dietary risk assessments were conducted.

Chronic dietary exposure to ETU from food alone ranges from 13 to 92% of the ADI for the different subpopulations and is not of concern. However, the chronic aggregate (food and water) exposure to ETU is 21 to 107% of the ADI, with the highest exposure in children 1 to 2 years of age. The acute exposure to ETU from food alone is 47% of the ARfD, with acute aggregate (food and water) exposure to ETU at 56% of the ARfD (95th percentile) for females aged 13 to 49 years, which is not of concern.

The ETU cancer risk from dietary exposure is 9×10^{-6} and 12×10^{-6} for food alone and food plus water respectively, which is of concern. A lifetime cancer risk that is below 1×10^{-6} (one in a million) usually does not indicate an unacceptable risk for the general population when exposure occurs through pesticide residues in or on food, and to persons otherwise unintentionally exposed. Further information on how the potential cancer risks from pesticides are assessed can be found in the Science Policy Notice SPN2000-01, *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*.

Occupational Risks from Handling Metiram

Occupational risks are not of concern provided that protective measures are followed.

Based on the precautions and directions for use on the original product label reviewed for this re-evaluation, risk estimates associated with mixing, loading and applying activities fail to reach the target MOE, and are of concern to the PMRA. Mitigation measures such as additional personal protective equipment, engineering controls, or restrictions on amount handled per day are required to reduce potential exposure and protect worker's health.

Postapplication Risks from Occupational Use of Metiram

Postapplication risks are of concern.

Post-application occupational risk assessments consider exposure to workers entering treated sites in agriculture. Based on the current use pattern for agricultural scenarios reviewed for this re-evaluation, postapplication risks to workers performing activities such as thinning, pruning, and harvesting of most crops, did not meet current standards and are of concern. Lengthened restricted-entry intervals (REIs) would be required to mitigate the risks to postapplication workers. However, as most of the proposed REIs are not considered agronomically feasible, lengthened REIs may not be viable risk mitigation options.

Environmental Considerations

What Happens When Metiram is Introduced Into the Environment?

Metiram poses a potential risk to birds, small wild mammals and aquatic organisms, therefore risk reduction measures need to be observed.

Metiram enters the the terrestrial and aquatic environments when it is applied as a fungicide on apples, potatoes, grapes etc. Once in the environment, it will transform rapidly through chemical reactions with water (hydrolysis) into a group of transformation products known as the metiram complex. The main transformation product in the complex is ETU which can transform further at a slower rate than parent metiram. Most of the chemical components of the complex partition onto soil and sediment particles and are not susceptible to phototransformation on soil and in water.

Biotransformation by microbial action is the main route of transformation of the metiram complex resulting in the release of transformation products including ETU into the environment. Significant portions of the complex remain associated with soil and sediment particles as non-extractable residues and are unlikely to release further ETU residues at environmentally significant levels. Metiram complex is classified as non-persistent in soil and moderately persistent in aquatic systems.

ETU is the common transformation product formed from metiram and other EBDC pesticides (such as mancozeb, maneb and nabam). It is not used for pest control like true pesticides. ETU forms via chemical reactions in water, through action of light and by microbial action after the application of metiram to the environment. ETU undergoes rapid breakdown in soil, through microbial action but the rate depends on the soil moisture levels and could be slightly to moderately persistent in soil. ETU generally does not bind strongly to soils and has high to very high mobility in soil, indicating it could reach surface water and groundwater. Canadian water monitoring data have confirmed ETU detections in surface water but not in groundwater.

Mobility of metiram complex in the natural environment is generally limited because of its strong affinity for adsorption to clay and organic matter fractions of the soils. In contrast, ETU is very soluble in water, mobile in soil, and can leach into groundwater and enter surface water in runoff. Metiram complex residues have a low potential to volatilize from dry or wet surfaces. Metiram complex is not expected to bioaccumulate in organisms. ETU may partition into air as indicated by its high vapour pressure, however, if it reaches air it is unlikely to be persistent ($T_{1/2}$ ranges from <2 hours to 9 days). ETU has a low potential for bioaccumulation in biota.

Metiram poses a potential risk to beneficial arthropods, birds, small wild mammals and to aquatic organisms. Small wild mammals and birds may be at risk of adverse reproductive effects due to consumption of contaminated food items, both at the site of application and off-field when exposed to residues from spray drift. Metiram residues from spray drift and runoff also pose risks to aquatic organisms. The risk of adverse effects, from exposure to metiram, to earthworms and bees are negligible.

Value Considerations

What is the Value of Metiram?

Metiram controls a broad range of economically important fungal diseases on a number of field crops.

Metiram is registered in Canada for use on several field and orchard crops to control a number of fungal diseases including the following economically important plant pathogens: downy mildew (*Plasmopara viticola*) on grapes, scab (*Venturia inaequalis*) on apples, early blight (*Alternaria solani*) and late blight (*Phytophthora infestans*) on tomatoes and potatoes, asparagus rust (*Puccinia asparagi*) on asparagus. Its use on seed borne common scab and Fusarium seed piece decay on potato seed pieces is no longer supported by the registrant. The most important uses of metiram include foliar treatments to control scab on apples, early and late blight on potatoes, and asparagus rust on asparagus.

Metiram is an important tool for resistance management in an integrated pest management program.

Metiram has been used in Canada since the 1960s on field and orchard crops. It is effective as a contact fungicide that controls the target pathogens upon direct contact and can be used as a protectant fungicide. Development of resistance in plant pathogens to this fungicide has not been reported in Canada to date. Metiram has a multi-site mode of action and, as such, fungal pathogens are not prone to the development of resistance. Due to this property, it is an important tool for resistance management in an integrated pest management (IPM) program where it is used as a rotational fungicide or as a tank-mix partner with other single-site modes of action fungicides which are at high risk for resistance development. Thus metiram helps to prolong the useful life of these single-site modes of action fungicides registered for similar uses.

Due to its multi-site mode of action, compatibility with other products, redistribution properties, and lower cost per treatment compared to other systemic fungicides, metiram has become one of the important chemicals in IPM programs in apples and potatoes. Metiram is also the only EBDC fungicide registered in Canada for control of asparagus rust on asparagus since the expiration of zineb as of 31 December 2010. Consequently, metiram is important to the production of asparagus, apple and potato in Canada.

Proposed Measures to Minimize Risk

Labels of registered pesticide product include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Based on available data and current assessments showing potential health and environment risks, Health Canada is proposing phase-out of all uses of metiram. During the phase-out of metiram, additional measures are proposed to reduce potential risks. These measures are discussed in the science section 9.1 of this Proposed Regulatory Decision.

Additional Risk-Reduction Measures

Human Health

To protect mixer/loaders/applicators:

- Additional Layer of protective equipment: Coveralls over a long-sleeved shirt, and long pants, and chemical-resistant gloves.
- Engineering Controls: Closed mixing and loading (for example, water soluble packaging), closed cabs for airblast application to apples and grapes, and open cab and respirator for groundboom application to asparagus, celery, tomato, carrot, sugar beets, and potatoes.
- Restrictions on the amount handled per day: Apples (airblast, 45 kg a.i./day), sugar beets, potatoes (groundboom, 125 kg a.i./day), and potatoes (aerial, 195 kg a.i./day)

To protect postapplication workers:

- Restricted Entry Intervals: Depending on the activity, lengthened REIs are required.

To mitigate potential aggregate risk from use of multiple EBDC pesticides:

- Additional label statement limiting applications of both mancozeb and metiram so that the total quantity of active does not exceed the specified maximum seasonal quantity for either mancozeb or metiram.

Environment

To reduce the release of metiram into the environment for the protection of habitats:

- Additional precautionary label statements and spray buffer zones to reduce runoff and protect non-target aquatic species.
- A statement advising that the use of metiram may result in leaching of ETU to groundwater particularly in areas where soils are permeable and/or the depth to the water table is shallow.
- The reduction of the maximum rates per application and the number of applications per year for better protection of non-target aquatic and terrestrial organisms.

What Additional Scientific Information Is Identified?

Based on available data and current assessments showing potential health and environmental risk concerns, Health Canada is proposing phase-out of all uses of metiram.

During the consultation period, the registrant may consider submission of data or propose changes to the use pattern that could be used to address risk concerns. The PMRA identified data that may help refine the risk assessments for metiram. These data are listed in section 9.2 of this Proposed Regulatory Decision.

Next Steps

Health Canada is proposing phase-out of all uses of metiram in Canada. During the transition, additional risk mitigation measures are proposed to reduce risks identified in this assessment.

As part of the consultation process, the registrant has the opportunity to propose changes to the use pattern and provide additional data to address the risk concerns. If additional scientific data and/or changes to the use pattern to address the risk concerns are not provided or fail to address the risk concerns, uses of metiram with risk concerns will be phased-out.

Before making a re-evaluation decision on metiram, Health Canada's Pest Management Regulatory Agency will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Science Evaluation

1.0 Introduction

Metiram is a broad spectrum, protectant fungicide with multi-site mode of action and belongs to Resistance Management Mode of Action Group M3. It belongs to the group of fungicides commonly known as ethylenebis(dithiocarbamate) fungicides (EBDCs), along with the active ingredients mancozeb, maneb, zineb and nabam. Of these, maneb has been voluntarily discontinued in Canada by the technical registrant and nabam has no food uses. Zineb is no longer registered in Canada.

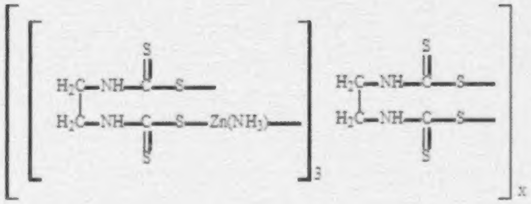
Following the re-evaluation announcement for metiram by the PMRA in the Re-evaluation Note REV2005-04, *PMRA Re-evaluation Program (April 2005 to June 2009)*, BASF Canada, the registrant of the technical grade active ingredient (TGAI) and primary data provider in Canada, indicated that it intended to continue to support all uses included on the label of the Commercial Class end-use product (EP), Polyram DF Water Dispersible Granular Fungicide (Registration No. 20087). The registrant no longer supports Polyram 16 Dust Fungicide (Registration No. 22029), a dust formulation, applied to foliage of potato, tomato, celery and grape, and the powder formulation of Polyram 16D Seed Piece Treatment (Registration No. 25867) applied to potato seed pieces for the control of Fusarium seed decay and seed-borne common scab. Polyram 16 Dust Fungicide is no longer registered in Canada; whereas, Polyram 16D Seed Piece Treatment will not be available for use in Canada after 31 December 2013.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Metiram
Function	Fungicide
Chemical Family	Ethylenedithiocarbamate
Chemical name	
1 **International Union of Pure and Applied Chemistry (IUPAC)**	Zinc ammoniate ethylenebis(dithiocarbamate)-poly(ethylenethiuram disulfide)
2 **Chemical Abstracts Service (CAS)**	Metiram
CAS Registry Number	9006-42-2
Molecular Formula	$(C_{16}H_{33}N_{11}S_{16}Zn_3)_x$

Structural Formula



Molecular Weight	$(1088.6)_x$
Purity of the Technical Grade Active Ingredient	89.0%
Registration Number	20084

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	**Result[1]**
Vapour pressure at 20°C	< 0.010 mPa
Ultraviolet (UV)/visible spectrum	Not expected to absorb at λ >300 nm
Solubility in water	N/A - Practically insoluble in water
n-Octanol/water partition coefficient	logP = 0.3 (pH 7)
Dissociation constant	N/A - No dissociable groups present

[1] Values from e-Pesticide Manual, version 3.1 (2004)

2.3 Description of Registered Metiram Uses

Appendix I lists all metiram products that are registered in Canada under the authority of the *Pest Control Products Act*. Appendix II lists all the uses for which metiram is presently registered and whether they are also supported by the registrant. Only uses supported by the registrant have been considered in the health and environmental risk assessments of metiram. Uses of metiram belong to the following use-site categories: Terrestrial Feed Crops and Terrestrial Food Crops.

3.0 Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

3.1 Toxicological Summary

Metiram

The toxicology database for metiram was lacking acute neurotoxicity and developmental neurotoxicity studies, as well as an adequate 2-generation reproductive toxicity study and a rabbit developmental toxicity study. However, the available toxicity data (Appendix IV, Table 1 and 2) have been used to select endpoints for risk assessment for dietary and non-dietary routes of exposure (Appendix IV, Table 2 and 3). Published studies have also been incorporated into the risk assessment. Refinements to the current risk estimates may be possible with the submission of additional toxicity data.

Metiram was readily absorbed by rats following low acute or repeat oral doses. Studies indicated that the processes leading to absorption of metiram in the gastrointestinal tract reach saturation at moderate to high dose levels, with peak plasma concentrations at 4 and 6 hours. Residues were primarily found in the thyroid and kidneys, with females having higher residue levels than males. Metabolites in urine, bile and kidney included ethylene diamine (EDA), N-acetyl-EDA, ethanolamine, oxalic acid, ethylene urea (EU), ethylene thiourea (ETU) and ethylene bis(isothiocyanate sulphide) (EBIS). Excretion was 98% complete within 48 hours (54-78% in feces and 21-47% in urine).

For the purposes of risk assessment, the extent of in vivo metabolic conversion of parent EBDC pesticide to ETU was determined to be 7.5% on a weight basis [United States Environmental Protection Agency (USEPA) 1989]. This value represents an average value for all EBDC pesticides (mancozeb, metiram, maneb, zineb, nabam). Based on urinary and biliary excretion of ETU in rat metabolism studies, about 20% of an administered EBDC dose is converted to ETU on a molar basis. In order to express the in vivo dose of ETU on a mg/kg bw basis, a molecular weight correction factor was applied. The molecular weight correction factor, 0.38, was calculated as the ratio of the ETU molecular weight (102 g/mole) and the average of all parent EBDC molecular weights (270 g/mole). Therefore, a 100 mg dose of an EBDC given to a rat would yield an in vivo ETU dose of 7.5 mg.

Metiram was of low acute oral, dermal and inhalation toxicity to mice and/or rats. It was non-irritating to rabbit eye and skin and it was a skin sensitizer in guinea pigs.

In short-term oral studies (mice, rats and dogs), the thyroid was the target organ after metiram exposure, with the dog being the most sensitive species. Thyroid effects included increased thyroid weights, decreased thyroxin (T_4) and increased triiodothyronine (T_3) values. Minimal to slight hypertrophy and vacuolation of the follicular epithelium of the thyroid was also observed. Reduced forelimb and hindlimb grip strength, ataxia and decreased areas of myelination in the sciatic, sural, and tibial nerves were noted in a short-term neurotoxicity study in rats.

Short-term inhalation toxicity studies in the rat caused a decrease in body-weight gain and increased intra-alveolar pigment deposition and mean lung/trachea weights. There was no effect on the thyroid through the inhalation route of administration.

Metiram was negative for gene mutation in both bacterial and mutation assays, with and without activation. It was also negative in structural chromosomal aberration and transformation assays, and unscheduled DNA synthesis with rat hepatocytes. In the assay for sister chromatid exchange (SCE) in Chinese hamster ovary cells (CHO), metiram induced increases in SCE over controls with and without mouse activation and without rat activation. However, the weight-of-evidence indicates that metiram is non-genotoxic.

Adequate chronic and oncogenicity studies were not available for metiram. However, since ETU is a common metabolite for all EBDCs, the ETU cancer risk assessment has been deemed appropriate for use in the metiram cancer risk assessment. For additional details, see the following ETU assessment.

The weight of evidence with respect to the current metiram chronic toxicity studies and the U.S National Toxicology Program (NTP) ETU study indicates that the thyroid, liver and pituitary are the primary targets of toxicity for both ETU and metiram. Although the metiram toxicity studies were considered supplemental for both cancer and systemic toxicity (because of various deficiencies), it is unlikely that new chronic and oncogenicity studies would provide any additional information to significantly inform the chronic and cancer risk assessments. Therefore, new chronic/oncogenicity studies for metiram are not required.

The rat reproduction toxicity study was considered supplemental since it lacked histology of the reproductive organs, results were highly variable through the three generations and the F3 pups were infested with nematodes. In the developmental toxicity study in rats, postimplantation loss was observed at a dose which caused a decrease in maternal body weight and body-weight gain. The rabbit developmental toxicity study was also considered supplemental, lacking a detailed examination of the fetal heads; however, no gross malformations were noted.

Evidence of neurotoxicity in short-term rat studies raises the concern for developmental neurotoxicity (DNT). Therefore, a DNT study is required. In addition, an acute neurotoxicity study, a developmental toxicity study in rabbits, and a two-generation reproduction toxicity study in the rat are also required. A 10-fold database uncertainty factor (UF_{DB}) is applied for the risk assessment of metiram to account for these deficiencies.

Epidemiology

The registrant did not submit any epidemiological studies for metiram. In addition, a search of published literature did not yield any studies. However, potential associations have been reported between the EBDC maneb (no longer registered in Canada) and Parkinson's Disease (PD), also referred to as Parkinson's-like Disease or Parkinsonism. Maneb is nabam plus elemental manganese, whereas metiram is nabam plus zinc and ethylenebisthiuram. The neurological effects noted with maneb may be related to the manganese content, as high concentrations of manganese can cause 'manganism', a disease similar to PD. In animal studies, co-administration of maneb and paraquat increased neurological effects in rats (Thiruchelvam et al. 2000, 2002, 2003, 2005; Barlow et al, 2003, Cicchetti et al, 2005, Cory-Slechta et al., 2004, 2005). Costello et al (2009) conducted a case-control study to examine the relationship between PD and residential exposure to paraquat and maneb in California, USA. Combined exposure to maneb and paraquat between 1974 and 1999 was associated with an increased risk of PD (OR=1.75, 95% 1.13, 2.73). However, this increase was mainly attributable to exposures between 1974 and 1989 (OR=2.14, 95% CI: 1.24, 3.68) as exposures between 1990 and1999 were not associated with an increased risk of PD (OR=0.93, 95% CI: 0.45, 1.94). Exposure to paraquat alone was not associated with an increased risk of PD and too few cases were exposed to only maneb to conduct a meaningful analysis. When stratified by age, PD risk was greatest among subjects with disease onset before 60 years of age. The reported findings suggest that combined exposure to paraquat and maneb may increase the risk of PD; however, this combination of exposures is no longer expected as maneb has been withdrawn by the registrant for use in Canada. Currently, epidemiological evidence does not establish a clear cause and effect relationship between a particular pesticide exposure and PD.

ETU

The toxicological database for ETU contains numerous published and unpublished studies, including metabolism, acute, short-term, long-term, reproductive, developmental and genotoxicity studies. However, for the purpose of this re-evaluation, the reproduction toxicity studies were considered supplemental and the database was lacking a developmental neurotoxicity study with comparative (adult vs. young) thyroid assay. Both unpublished and published data have been considered in the toxicity assessment.

ETU was rapidly absorbed in the digestive tract, and relatively slowly absorbed via the skin. Regardless of absorption pathway, ETU primarily accumulated in the thyroid, followed by the kidney, liver and brain. It had an elimination half-life of approximately 28 hours in the monkey, 9 to 10 hours in the rat and 5 hours in the mouse. Excretion was complete and occurred primarily in the urine (50 to 80%, depending on the species). Metabolism was more rapid in the mouse than in the rat, but more extensive in the rat with metabolites consisting of ethylene urea and other polar compounds.

During gestation, ETU in amniotic fluid, placenta and fetal carcass correlated with maternal blood levels. In postpartum animals, ETU levels in maternal liver and milk were 10-fold and 2-fold greater than maternal blood, respectively. Levels in maternal milk were 13-fold greater than in neonatal animals. Following oral exposure, blood levels peaked in maternal mice and rats after 1.3 and 1.4 hours, respectively and in the fetus after 2 hours. The main route of excretion was urine, with 74% of administered dose in the mouse and 70% of administered dose in the rat. In the mouse, 40% of ETU was metabolized, versus 95% in the rat. Oral administration in mice induced cytochrome P-450 (aniline hydroxylase: CYP2E1), but this activity was reduced in rats. This metabolic difference may be the reason that fetal rats demonstrate severe toxicity while the fetal mouse demonstrates mild toxicity, at comparable dose levels.

In published studies and assessments, ETU was of low acute oral toxicity in non-pregnant and pregnant mice (tested on gestation day 9) and pregnant hamster (tested on gestation day 11) and of low to moderate toxicity in non-pregnant and pregnant rats (tested on gestation day 13), respectively. ETU was of low acute dermal toxicity in the rabbit and low acute inhalation toxicity in the rat. It was non-irritating to rabbit eye and skin and was a skin sensitizer in guinea pigs.

The primary effects of ETU in mice and rats after short-term oral exposure were observed in the thyroid (decreased T_4, increased TSH, increased weight and hyperplasia) and liver (increased weight, cytoplasmic vacuolation, and hyperplasia). Although mice exhibited thyroid effects, these occurred at higher dose levels than in the rat. However, mice were more sensitive to the liver effects than the rat. In 90-day and 1-year dog studies, body weight and blood effects, indicative of hemolytic anaemia (decreased haemoglobin, packed cell volume, red blood cells and increased reticulocytes), occurred at lower or at the same dose levels causing thyroid toxicity. Short-term dermal and inhalation toxicity studies were not available.

The United States NTP conducted reproductive/chronic/oncogenicity studies in the mouse and rat, combining both perinatal and adult exposures to ETU. Similar to the short-term studies, the thyroid, liver and pituitary were primary targets after exposure to ETU. Although the weight-of-evidence suggested that ETU was weakly genotoxic, thyroid tumours in both the mouse and rat had a clear mode and mechanism of action. ETU inhibits thyroid peroxidase, leading to chronic thyroid hormone deficiency (decreased T4). This in turn stimulates the hypothalamus and pituitary, causing the production of more thyroid stimulating hormone (TSH). This hormonal imbalance could lead to thyroid growth, hyperplasia and subsequent follicular cell neoplasia. Frequently, pituitary gland neoplasia also occurs, which was evident with ETU exposure in the mouse. Similar to the short-term studies, the mouse was more sensitive to liver effects than the rat in long-term studies. In the NTP study, mice exhibited an increase in liver adenomas and carcinomas, showing a clear dose-response in females. These adenomas/carcinomas occurred at comparable or lower doses than the thyroid and pituitary tumours. Since there is no current evidence supporting a threshold for induction of liver tumours, a cancer unit risk (q_1^*) of 0.0601 (mg/kg bw/day)$^{-1}$ based on liver tumours was generated for the cancer risk assessment of ETU and all EBDCs.

There were two supplemental reproduction toxicity studies in the ETU database. In one study, dose levels in mg/kg bw/day could not be calculated because of stability problems with the test material and unknown feed consumption. In addition, the study did not account for all of the pups. In the second study, there were low pup numbers. Both of these studies identified the thyroid as the primary target in adult rats and mice and decreased survival in both rat and mouse pups.

Developmental toxicity occurred via both the oral and dermal routes of exposure, with rats being the most sensitive species. After dermal exposure on gestation days 12 to 13, all fetal rats had marked skeletal malformations, at non-maternally toxic doses. The developmental effects by both the oral and dermal routes of exposure included cryptorchidism, exencephaly, ectopic kidneys, agenesis of kidneys, hydronephrosis, edematous fat pads, less than 13 ribs, fused lumbar, sacral or caudal vertebrae, oligodactyly, syndactyly, webbed digits, anal atresia and malformation of the central nervous system.

Although thyroid toxicity is often associated with developmental effects, this potential mode of action is not applicable to the acute exposures that resulted in the above-noted malformations, indicating that ETU was a direct developmental toxin in the rat. In published studies, no developmental effects were noted in hamsters or guinea pigs. In mice, the only developmental effect observed was an increase in supernumerary ribs. Cats exhibited malformations in their offspring, at maternally toxic doses. Rats may have a differential sensitivity because of the way ETU is metabolized, compared to the mouse, rabbit, hamster, guinea pig and cat.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food, handling the pesticide or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

Metiram

With respect to potential pre- and postnatal toxicity, a serious endpoint of concern was observed in the rat developmental toxicity study as evidenced by pre- and postimplantation loss at a dose level that produced maternal toxicity (decreased body weight gain and body weight). The currently available rabbit developmental toxicity study lacked a detailed examination of the head and the available 3-generation reproduction toxicity study lacked histology of reproductive organs and had highly variable results. However, the residual concern for pre/postnatal toxicity is tempered by the fact that the dose-response in the rat developmental toxicity study is well characterized, with clear NOAEL/LOAELs for maternal and developmental toxicity, that developmental effects in the supplemental rabbit developmental toxicity study were noted in the presence of maternal toxicity and the NOAELs selected for the overall risk assessment were 1.5 to 20 fold lower than the NOAEL for the effects observed in the rabbit developmental toxicity study. It is anticipated that uncertainties relating to the completeness of data with respect to the toxicity to infants and children are addressed through the application of a 10-fold uncertainty factor for database deficiency (UF_{DB}). Thus, based on these considerations, the PCPA factor was reduced to 1-fold.

ETU

While there are no pesticide registrations for ETU, it is a metabolite of EBDC fungicides. The ETU database contains both unpublished and published studies, but lacks an adequate rat reproduction study and a rat developmental neurotoxicity (DNT) study, with a comparative thyroid assay. These studies will be required for the continued registration of EBDC fungicides.

With respect to pre- and post-natal toxicity, sensitivity of the young was observed in numerous rat developmental studies. Multiple and serious head, central nervous system and skeletal malformations were noted after 1-2 doses via both the dermal and oral routes of exposure. The effects occur at non-maternally toxic doses. ETU was also developmentally toxic to the rabbit, but at higher dose levels than seen with the rat. A published cat study demonstrated less severe developmental toxicity at doses similar to the rat, but these dose levels were also maternally toxic.

Although sensitivity of the young was identified in developmental toxicity studies, the potential for reproductive and developmental neurological effects has yet to be characterized. Considering the database deficiencies with respect to toxicity in the young, and the serious developmental effects that occur at non-maternally toxic doses, the PCPA factor of 10-fold will be retained for those exposure scenarios that refer to the NOAEL for malformations in the risk assessment. The use of the NOAEL for thyroid toxicity in the one-year dog study as a point of departure for long term exposure scenarios provides an adequate margin to levels which caused developmental toxicity. Therefore, the PCPA factor was reduced to 3-fold when the one-year dog study is the reference study for risk assessment.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

Where evidence of carcinogenicity is identified for the active ingredient, a cancer potency factor (q_1^*) is generated and used to estimate cancer risk. The product of the expected exposure and the cancer potency factor (q_1^*) estimates the lifetime cancer risk as a probability. A lifetime cancer risk of 1 in 10^{-5} in worker populations and 1 in 10^{-6} in the general population is generally considered acceptable. Further information on how the potential cancer risks from pesticides are assessed can be found in the Science Policy Notice SPN2000-01, *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*.

3.2.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment

3.2.1.1 Metiram short- and intermediate-term dermal risk assessment

For short and intermediate-term dermal risk assessment, a 90-day neurotoxicity study in rats was selected. A NOAEL of 6.7 mg/kg bw/day was established, with neuromuscular effects observed at the LOAEL of 23.5 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional 10-fold database uncertainty factor was also applied due to the lack of a number of core studies. The target MOE is 1000, which protects worker populations that could include pregnant or lactating women.

3.2.1.2 Metiram short- and intermediate-term inhalation

For short-, and intermediate-term inhalation risk assessment, a 90-day inhalation study was selected for risk assessment. A NOAEL of 0.5 mg/kg bw/day was established, with decreased body weight gain observed at the LOAEL of 5 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional 10-fold database uncertainty factor was also applied due to the lack of a number of core studies. The target MOE is 1000, which protects worker populations that could include pregnant or lactating women.

3.2.1.3 ETU short- and intermediate-term dermal and inhalation

To estimate short and intermediate-term dermal and inhalation risk, numerous rat developmental toxicity studies were considered. At doses of 10 mg/kg bw/day and greater, increased head and skeletal malformations were observed at non-maternally toxic doses. A NOAEL of 5 mg/kg bw/day was established. Worker populations could include pregnant or lactating women and therefore this endpoint was considered appropriate for occupational risk assessment. The target MOE for these scenarios was 1000, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. Since the malformations noted are serious, occur at non-maternally toxic doses, and to address residual concerns related to database uncertainties, an additional 10-fold factor was applied to protect the pregnant worker, an identified sensitive sub-population.

3.2.1.4 ETU Cancer Potency Factor

A published study by the NTP examined the oncogenic potential of ETU in mice and rats. This study was considered a generational study since it examined the effects of ETU exposure on animals during gestation and for 2 years following parturition. Since there is no current evidence supporting a threshold mode of action for liver tumour induction in female mice, a q_1^* of 0.0601 (mg/kg bw/day)$^{-1}$ was calculated and used for the cancer risk assessment of ETU and all EBDCs.

3.2.1.5 Dermal Absorption

Based on chemical-specific in vivo dermal absorption studies, dermal absorption factors of 7% and 45% were determined for risk assessment purposes of metiram and ETU, respectively.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to metiram through mixing, loading or applying the pesticide, and when entering a treated site to conduct activities such as scouting and/or irrigating treated crops.

Ethylene thiourea is a contaminant of metiram formulations, a degradate of metiram that can be formed in tank mix solutions, and it can also be formed in the body from the metabolic conversion of metiram. Potential exposure was also quantified for ETU. To estimate the amount of ETU that can potentially be formed in the tank mix, a value of 0.1% was used based on tank mix stability studies summarized in the USEPA RED (2005). The amount of ETU formed in vivo was estimated by assuming that 7.5% of absorbed metiram would be transformed into ETU (see Section 3.1). To estimate postapplication exposure to ETU, direct measurements of ETU were taken in the dislodgeable foliar residue (DFR) study. For handlers, total ETU exposure was estimated by summing exposure from its presence in the tank mix and the amount formed from handler metabolism of metiram. For postapplication workers, total exposure was estimated by summing exposure from the foliage using the DFR study and the amount formed as a result of worker metabolising metiram.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders and applicators. The following supported uses were assessed:

- Open mixing and loading of dry flowables (wettable dispersible granule);
- Mixing/loading of wettable powders packaged in water soluble packaging (used to approximate wettable dispersible granules packaged in water soluble packets);
- Airblast application (open and closed cab) to apples and grapes;
- Groundboom application (open and closed cab) to potato, sugar beets, asparagus, carrots, celery, and tomato;

Due to the number of agricultural applications per year (ranging from 2 to 10), exposure is likely to be short-to-intermediate term (that is, up to several months) in duration.

ETU is a contaminant of metiram formulations and a degradate that can be formed in tank mix solutions. To estimate the amount of ETU that can potentially be formed in the tank mix, tank mix stability studies were submitted and evaluated by the USEPA (2005 RED). Several major limitations with the data were noted. In the absence of any additional data, a value of 0.1% was used to estimate the amount of ETU that is formed in tank mixes of metiram during mixing/loading and application. A value of 0.1% was also used to estimate ETU exposure when handling dry formulations. Additional confirmatory data is necessary.

For agricultural crops, the PMRA estimated handler exposure for several scenarios including mixer/loader/applicators wearing coveralls over a single layer of clothing and chemical-resistant gloves (except for applicators using groundboom equipment), open and closed mixing and loading, and applicators using groundboom or airblast equipment with open and closed cabs.

Dermal and inhalation exposures were estimated using data from the *Pesticide Handlers Exposure Database (PHED), Version1.1*. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment (PPE). In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing coveralls or a respirator; this was estimated by incorporating a 75% clothing protection factor, and a 90% protection factor for a respirator.

3.2.2.1.1 Occupational Exposure Non-Cancer Risk Estimates – Metiram

Route specific MOEs for mixer/loaders and applicators for agricultural crops are outlined in Appendix V, Table 1.

Based on the PPE recommended on the label (long-sleeved shirt, long pants, and chemical-resistant gloves), route-specific MOEs range from 33 to 963 for apples, asparagus, carrot, celery, grapes, potato, sugar beets, and tomato. With engineering controls (in other words, closed mixing and loading (water soluble packaging) and closed cab or open cab with respirator), an additional layer of PPE (that is, coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves), and restrictions on amount handled per day for apples, sugar beets and potatoes, calculated MOEs exceed the target MOE, and are not of concern.

3.2.2.1.2 Occupational Exposure Non-Cancer Risk Estimates – ETU

Combined MOEs for mixer/loaders and applicators for agricultural crops are outlined in Appendix V, Table 2.

Calculated ETU MOEs for mixer/loaders and applicators of metiram to agricultural crops exceeded the target MOE with the mitigation measures outlined above for metiram, and are not of concern.

3.2.2.1.3 Occupational Exposure Cancer Risk Estimates

The cancer risk for occupational workers was determined by calculating the lifetime average daily dose (LADD) from the total ETU exposure. The LADD was then multiplied by the q_1^* to obtain cancer risk estimates. Occupational cancer risk is calculated assuming 40 years of exposure (for example, a career in agriculture of 40 years) over a 75-year lifetime. Farmer applicators were considered to be exposed 2 – 10 days per year and custom applicators were assumed to be exposed for 30 days per year based on the maximum number of applications per year, and professional judgement, respectively. The product of the LADD and the q1* estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-5} to 1 in 10^{-6} or less in worker populations is generally acceptable.

For agricultural crops, lifetime cancer risk estimates associated with mixing/loading/applying metiram with the mitigation measures outlined in Section 3.2.2.1.1, are not of concern. Appendix V, Table 3 summarizes the calculated cancer risk for mixers/loaders and applicators.

3.2.2.2 Post-application Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (such as pruning, thinning, harvesting, or scouting). Based on the metiram use pattern, there is potential for short- to intermediate-term (>1 day - several months) postapplication exposure for the majority of scenarios.

Potential exposure of postapplication workers was estimated using activity-specific transfer coefficients (TCs) and dislodgeable foliar residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard agricultural work clothing worn by adult workers. Post-application exposure activities include harvesting, thinning, pruning, scouting and irrigating.

A chemical-specific DFR study was available that quantified DFR for metiram and ETU. The study was conducted in apples in California. Using the results from this study, peak residues of 10% of the application rate for metiram and 0.15% for ETU were used to estimate potential exposure immediately following application. The dissipation of metiram (2.3%) and ETU (1.7%) was then estimated using the percent dissipation per day calculated from the linear equation of plotting the natural logarithm (ln) of DFR versus dissipation time (postapplication interval). This study was also used to estimate residues on all agricultural crops. There is some uncertainty in this approach, as the application rate, foliage type, application equipment and crop morphology in the study may not be representative of all crops; however, it is the best data available at this time.

Total ETU exposures were calculated by summing exposure to ETU from its presence on foliage and the amount as a result of workers metabolising metiram. A value of 7.5% was used to estimate the amount of absorbed metiram that is metabolized to ETU as described in Section 3.1.

3.2.2.2.1 Post-application Worker Non-Cancer Exposure and Risk Assessment – Metiram

Post-application exposure is expected to be short-to-intermediate term in duration (>1 day – several months).

For workers entering a treated site, restricted entry intervals (REIs) are calculated to determine the minimum length of time required before people can enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE.

Post-application exposure and risk estimates are presented in Appendix V, Table 4. The restricted entry intervals required to reach the target MOE range from 27 to >175 days, except for a few minor contact activities. In the case of hand harvesting scenarios, the REI is greater than the preharvest interval for all crops. These REIs are not considered to be agronomically feasible.

3.2.2.2.2 Post-application Worker Non-Cancer Exposure and Risk Assessment – ETU

Calculated ETU MOEs are presented in Appendix V, Table 5.

Calculated REIs required for the ETU MOE to reach the target MOE range from 12 hrs to 163 days. All of the REIs required to mitigate exposure to ETU are less than the REIs calculated in the previous section for metiram.

Further data, as described in section 9.2, may refine the assessment and reduce the length of the REIs calculated for metiram. However, it should be noted, that even if the postapplication exposure assessment is refined with additional DFR data and use pattern information, calculated REIs required to mitigate ETU exposure might still be considered agronomically unfeasible. Most of the calculated MOEs for ETU on day 0 are considerably less than the target MOE of 1000 (range from 45 to 721, except for some minor contact activities), and given the relative persistence of metiram and ETU residues, it is unknown whether additional information will result in calculated ETU REIs that are agronomically feasible.

3.2.2.2.3 Post-application Worker Cancer Exposure and Risk Assessment

Exposure to postapplication workers was based on average residues for a 30 day period starting on the day of the recommended REI for metiram and ETU, as specified in Appendix V, Table 4 and 5, respectively. It was assumed that postapplication workers would perform each activity for a period of 30 days. Cancer risks were calculated using a linear low-dose extrapolation approach, in which a LADD was calculated and then multiplied by a q_1^* that had been calculated for ETU based on dose response data in the appropriate toxicology study ($q_1^* = 0.0601$ (mg/kg bw/day)$^{-1}$).

The total ETU absorbed daily dose on the REI day established in Section 3.2.2.2.1 or 3.2.2.2.2 is based on direct exposure to ETU residues on the REI day and metabolic conversion of metiram exposures on the REI day.

Cancer risk is presented in Appendix V, Table 6. All calculated cancer risks are less than or equal to 1×10^{-5}, and are not of concern, due primarily to the fact that proposed REIs for non-cancer risk are very long. Should data be submitted to reduce these REIs (see above), the cancer risks may increase at the lower REI. Information that could refine the cancer risk assessment includes: use pattern information such as typical application rates, typical number of applications, total number of days of possible exposure for postapplication activities for each crop and their co-occurrence with application of metiram, and typical lifetime working durations of postapplication workers. The cancer risk assessment based on interim REIs will need to be re-assessed following consultation.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to metiram from potentially treated imports is also included in the assessment.

These dietary assessments are age-specific and incorporate the different eating habits of the population at various stages of life. For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting the use of a pesticide when its risk exceeds 100% of the reference dose. Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessments procedures. A lifetime cancer risk that is below $1x\ 10^{-6}$ usually does not indicate an unacceptable risk for the general population when exposure occurs through pesticide residues in or on food, and to person otherwise unintentionally exposed.

Residue estimates used in the dietary risk assessment may be conservatively based on the maximum residue limits (MRLs). They may also be based on the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program. However, residue data suitable for the purpose of the metiram dietary risk evaluation were not available from these programs.

The dietary risk assessment considered exposure from all food and water sources that could potentially contain metiram or ETU. Residue estimates for animal commodities were based on feed residue data, while residue estimates for most plant commodities were based on field trial data. When field trial data were not available, the general MRL or American tolerances were used to estimate residues in crops. Processing factors, % of crop treated (CT) and food supply information was also used in the assessment where applicable. The field trial studies available were generally not conducted in the Canadian regions and/or according to the Canadian good agricultural practice (GAP). In fact, some of these field trials were conducted using lower rates than used in Canada. Thus, there is uncertainty in the food residue data used to estimate exposure and concern that dietary exposures are underestimated. Additional field trial data conducted in accordance with the Canadian use pattern may address these uncertainties.

In situations where the need to mitigate dietary exposure has been identified, the following options are considered. Dietary exposure from Canadian agricultural uses can be mitigated through changes in the use pattern. Revisions of the use pattern may include such actions as reducing the application rate or the number of seasonal applications, establishing longer preharvest intervals, and/or removing uses from the label. In order to quantify the impact of such measures, new residue chemistry studies which reflect the revised use pattern are required. These data would also be required in order to amend MRLs to the appropriate level. Imported commodities which have been treated also contribute to the dietary exposure, and are routinely considered in the risk assessment. The mitigation of dietary exposure that may arise from treated imports is generally achieved through the amendment or establishment of MRLs.

Acute, cancer and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14) which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendix VI, VII and VIII.

3.3.1 Determination of Acute Reference Dose

Metiram

Acute Reference Dose (ARfD), Females 13-49 Years of Age

To estimate acute dietary risk (1 day), for females 13-49 years of age, the NOAEL of 80 mg/kg bw/day from the guideline rat developmental toxicity study was selected for the risk assessment. At 160 mg/kg bw/day, an increase in postimplantation loss was observed in the presence of decreased maternal body weight and body weight gain. Since some of the animals, at termination, only had placenta without fetal tissue visible, the postimplantation loss appeared to have occurred at both early and late time points. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional 10-fold database uncertainty factor was also applied due to the lack of a number of core studies. As discussed in section 3.1, the PCPA factor was reduced to 1-fold, making the composite assessment factor 1000, which is considered protective of sensitive sub-populations.

$$\text{ARfD} = \frac{\underline{80\ \text{mg/kg bw/day}}}{1000} = 0.08\ \text{mg/kg bw/day}$$

Acute Reference Dose (ARfD), General Population (including children)

An ARfD for the general population was not established as there were no acute endpoints of concern identified in the current database.

ETU

Acute Reference Dose (ARfD), Females 13-49 Years of Age

To estimate acute dietary risk (1 day), numerous rat developmental toxicity studies were considered. At doses of 10 mg/kg bw/day and greater, increased head, CNS and skeletal malformations were observed at non-maternally toxic doses. A NOAEL of 5 mg/kg bw/day was established. Standard uncertainty factors, 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in section 3.1, the 10-fold PCPA factor has been retained. The composite assessment factor is 1000.

$$\text{ARfD} = \frac{\underline{5\ \text{mg/kg bw/day}}}{1000} = 0.005\ \text{mg/kg bw/day}$$

Acute Reference Dose (ARfD), General Population (Including Children)

An ARfD for the general population was not established as there were no acute endpoints of concern identified.

3.3.2 Acute Dietary Exposure and Risk Assessment

Acute dietary risk is calculated considering the highest ingestion of metiram and ETU that would be likely on any one day, and using food consumption and food residue values. A statistical analysis compiles all possible combinations of consumption and residue levels to estimate a distribution of the amount of metiram and ETU residue that might be consumed in a day. A value representing the high end (95th percentile) of this distribution is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, then acute dietary exposure is not of concern.

Metiram

The acute dietary exposure estimates of metiram from food accounted for less than 88% of the ARfD for females 13 to 49 years of age.

ETU

The acute dietary exposure estimates of ETU from food accounted for less than 47% of the ARfD for females 13 to 49 years of age.

3.3.3 Determination of Acceptable Daily Intake

Metiram

To estimate dietary risk from repeat exposure, a one-year dog study was selected for risk assessment. At 29.8 mg/kg bw/day, effects on the thyroid and thyroid hormones were observed. A NOAEL of 2.5 mg/kg bw/day was established. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 10-fold database uncertainty factor was also applied due to the lack of a number of core studies. As discussed in section 3.1, the PCPA factor was reduced to 1-fold, resulting in a composite assessment factor of 1000, which is considered protective of sensitive sub-populations.

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.5 \text{ mg/kg bw/day}}{1000} = 0.0025 \text{ mg/kg bw/day}$$

This ADI is considered to be protective of all sub-populations including infants and children and provides a margin of 4000 to the NOAEL for abortions noted in the supplemental rabbit study.

ETU

To estimate dietary risk from repeat exposure, a one-year dog study was selected. At the LOAEL of 1.79 mg/kg bw/day, decreased body weight and increased thyroid weight, hypertrophy and colloid retention were observed. A NOAEL of 0.18 mg/kg bw/day was established. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in section 3.1, the PCPA factor of 10-fold was reduced to 3-fold. The composite assessment factor of 300 provides adequate protection for sensitive sub-populations.

$$\text{ADI} = \frac{0.18 \text{ mg/kg bw/day}}{300} = 0.0006 \text{ mg/kg bw/day}$$

This ADI provides a margin of greater than 8000 to the NOAEL for developmental malformations noted in the rat.

3.3.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic dietary risk is not of concern.

The chronic deterministic dietary exposure assessment was based on residue data from crop field trials, food residue data from an industry sponsored EBDC/ETU market basket survey (MBS) conducted in the United States, processing factors, percentage of treated crops as well as percentage of imported commodities. The default MRL of 0.1 ppm for metiram was used for crops appearing on registered labels without a specified MRL. The MRL of 0.05 ppm for ETU specified under B.01.046 and B.01.047 of the *Food and Drug Regulations* was used for crops appearing on registered labels without any ETU residue data.

The risk assessment was refined through the use of field trial residue data, processing factors, and estimates of the percentage of treated crops as well as percentage of imported commodities. Uncertainty in the risk assessment exists through the use of residue data obtained from field trials performed outside Canadian regions at rates lower than the Canadian GAP.

Metiram
The dietary exposure estimates from food ranged from 8 to128% of the ADI and is of concern. Children aged 1 to 2 had the highest exposure. The driving commodities for exposure are grapes accounting for up to 51% of the ADI in the dietary assessments.

ETU
The dietary exposure estimates from food accounted for less than 92% of the ADI for all subpopulations, including the most affected subpopulation of children aged 1 to 2 years; and is, therefore, not of concern. The driving commodities for exposure are the grape commodities accounting for up to 44% of the ADI in the dietary assessments.

3.3.5 Cancer Potency Factor q_1^*

ETU
As discussed in section 3.1, a unit risk q_1^* of 0.0601 (mg/kg bw/day)$^{-1}$, obtained from the U.S. National Toxicology Program study for ETU, is deemed appropriate for assessing the dietary cancer risk for metiram. The amount of ETU formed *in vivo* was estimated by assuming that 7.5% (see Section 3.1) of absorbed metiram would be transformed into ETU.

3.3.6 Cancer Dietary Exposure and Risk Assessment

The lifetime cancer dietary risk for ETU was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then multiplied by the q_1^* to determine the cancer risk. A lifetime cancer risk that is below $1x\ 10^{-6}$ usually does not indicate an unacceptable risk for the general population when exposure occurs through pesticide residues in or on food, and to person otherwise unintentionally exposed.

Similar to the chronic dietary exposure assessment, the cancer assessment was based on the residue data from field trials, residues from the MBS, processing factors, percentage of treated crops as well as percentage of imported commodities. The ETU MRL of 0.05 ppm was used for crops without residue field trials.

Based on the q_1^* approach, the lifetime cancer risk for ETU from food-only exposure was determined to be 9×10^{-6}, for the general population and is of concern.

As in the chronic risk assessment, the risk assessment was refined to the extent possible using the data available. This included the use of processing factors, percentage of treated crops as well as percentage of imported commodities. Uncertainties in the risk assessment include the use of residue data obtained from field trials performed outside Canadian regions and which were less than the Canadian GAP.

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Metiram is similar in its environmental fate to closely related compounds such as maneb and mancozeb. They are of low persistence and are strongly bound to most soils. These properties, and their low water solubilities, indicate that they probably do not pose a significant risk to groundwater. They are unstable in the presence of atmospheric moisture and oxygen and are rapidly degraded in biological systems to ETU and other metabolites. These products are of moderate persistence and more mobile, and therefore may pose a slight risk to groundwater. ETU is not applied directly in the environment. It exists in the soil as the common transformation product of applied parent EBDC fungicides, which include mancozeb, metiram, and nabam. As metiram is of low persistence in water supplies, the only residue of concern in drinking water is the primary metabolite, ETU.

Estimated environmental concentrations (EEC's) of ETU in potential drinking water sources (surface water – reservoir and dugout) were estimated based on the total EBDC use pattern, using computer simulation models. For residues in reservoir, refined exposure concentrations predicted by PRZM/EXAMS were estimated to be 16 µg a.i./L and 2.9 µg a.i./L for the daily and yearly concentrations, respectively. These values were used in the dietary assessment of ETU.

3.4.2 Drinking Water Exposure and Risk Assessment

As indicated in 3.4.1, ETU is the only metabolite of metiram expected to be found in drinking water supplies. In the cancer and chronic assessment, residues in drinking water were based on the reservoir yearly EEC (2.9 µg a.i/L), whereas in the acute exposure the residues were based on the daily EEC (16 µg a.i/L). The calculated chronic exposure of ETU from drinking water alone reached an interval of 7 to 33% of the ADI for all subpopulations, below the level of concern. The acute estimation for drinking water accounted for 16% of the ARfD for the female 13 to 49 years subpopulation and is not of concern. The cancer risk estimation from drinking water attained 4×10^{-6} and is of concern.

3.5 Aggregate Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal and inhalation).

As metiram is not registered for residential and non-occupational uses, the aggregate risk assessment considered exposure to metiram and ETU from food and drinking water only. Metiram is not expected to occur in drinking water. Therefore, food-only exposure was considered for metiram and was determined to be of concern for chronic exposure (refer to Section 3.3.4). For ETU risk from food and drinking water, refer to Section 3.4.2.

Aggregate dermal and dietary risk assessments for Pick-Your-Own and residential bystander exposure from fruit tree applications was not conducted, as occupational postapplication exposure is of concern.

3.6 Cumulative exposure and risk assessment

Exposure to ETU in food and drinking water may also occur from the use of mancozeb or any other EBDC fungicides. Presently, mancozeb is the only other EBDC fungicide with registered food uses in Canada, while nabam is registered in Canada for industrial uses only.

Exposure to ETU in the environment or in occupational settings may occur from non-pesticidal sources of ETU. These sources are regulated separately (*Canadian Environmental Protection Act, 1999*) from the exposure derived from the pesticidal use.

As the aggregate exposure from food and water to metiram alone and ETU derived from metiram is of concern, a combined/cumulative risk assessment was not conducted at this time. It is acknowledged that the drinking water exposure estimates do represent the total exposure from ETU from all pesticidal sources (mancozeb or metiram). However, as the aggregate risk for metiram and mancozeb are estimated independently, this approach does not over-estimate the risk. Furthermore the use pattern on which the water modelling was performed is identical for metiram and mancozeb.

To mitigate potential aggregate risk from use of multiple EBDC pesticides, the following label statement is proposed to be added to the labels of mancozeb and metiram during the phase out of metiram:

> "Total quantity of all EBDC products used on a crop must not exceed the specified maximum seasonal quantity of active ingredient allowed per hectare for either mancozeb or metiram."

3.7 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failures. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc. to major effects such as reproductive or developmental effects, life-threatening conditions or death.

The PMRA examines incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures are taken, ranging from minor label changes to discontinuation of the product.

As of 15 November 2012, there were 2 scientific study incidents and 1 human incident with the severity classification of moderate relating to Polyram DF, an end-use product containing metiram. The human incident report was from an occupational incident and symptoms of skin sensitization following an acute exposure were reported. No domestic animal, environment or packaging failure incidents involving the active ingredient metiram were reported to the PMRA.

Since ETU is not a registered active ingredient, incident reports identifying ETU specific adverse events are not expected.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Metiram is a high molecular weight polymer that breaks down rapidly (half-life from 33 to 75 hours) through hydrolysis into the metiram complex, a suite of chemicals that includes residues of variable/low molecular weight polymeric chains. The main transformation products in the complex are ethylene thiourea (ETU) and CO_2.

Metiram complex has low solubility in water (< 2 mg/L at 20°C). The Henry's Law constant ($<5.4 \times 10^{-3}$ Pam^3/mole at 20° C) indicates that metiram complex is non-volatile from moist soil and water surface. Metiram complex in soil and water is stable to hydrolysis and photolysis.

Biotransformation is the main route of transformation of metiram complex in soil and water. Major transformation products obtained from the biotransformation of metiram complex in soil are ETU, EBIS, TDIT and CO_2. ETU breaks down further to EU. ETU is a common transformation product of the EBDC group of fungicides, of which mancozeb, metiram and nabam are members. The PMRA expects that ETU produced from mancozeb's use pattern will exceed that from metiram, being that mancozeb has the broadest use pattern of all the EBDC fungicides in Canada.

ETU is shown to be stable to hydrolysis and phototransformation in sterile aqueous solutions and soil media. However, there is evidence indicating that sensitizers in natural waters result in rapid indirect photolysis of ETU via a catalyst process (a half-life in aqueous solutions of 2.3 d was found for sensitized water). ETU is expected to partition in the air as indicated by its high vapour pressure, however, it will not remain in air as it has a half-life ranging from <2 hours to 9 days as it reacts with hydroxyl radicals in the atmosphere. Once present in the soil environment ETU will undergo rapid aerobic biotransformation however, a slight decrease in the rate of biotransformation is expected with a reduction of available soil moisture. ETU is slightly to moderately persistent in soil. ETU generally does not bind strongly with soils and has high to very high mobility and has a potential to move to surface water and to leach to groundwater, however, it was not detected below 15 cm in two field studies. ETU residues have not been detected in groundwater in Canada, but has been in the U.S. Residues of ETU have been detected in surface water in Canada (Appendix X).

During biotransformation, significant portions (5.7 to 90%) of the complex can remain associated with soil and sediment particles as non-extractable residues. Under aerobic laboratory conditions, metiram complex was found to be non-persistent in soil with DT_{50} values that ranged from 1.9 to 13.6 days. Under field conditions, metiram complex is moderately persistent in soil with a DT_{50} of 135 days and ETU is slightly persistent with a DT_{50} of 30 d. Metiram complex is moderately persistent in aerobic aquatic systems (water and sediments) with DT_{50s} in the range of 56.9 to 178 days.

Metiram complex has low mobility in most soils in view of its strong adsorption to clay (K_{oc} 111) and organic fractions but has weak adsorption to sand (K_{oc} 1738). ETU adsorbs weakly to soil and thereby moves through soil and has a potential to leach into groundwater and runoff to surface water.

The log K_{ow} of 1.92 indicated that metiram complex has a low potential for bioaccumulation in biota. Environmental fate data for metiram are summarized in Table 1 of Appendix IX.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (for example, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Data derived from monitoring studies may also be used in refining a risk assessment (Appendix X).

4.2.1 Risks to Terrestrial Organisms

A risk assessment of metiram complex to terrestrial organisms was based upon evaluation of toxicity data for the following (Table 2, Appendix IX):

- one earthworm species, one bee species and four other arthropod species representing invertebrates (acute and long-term exposure)
- two bird and one mammal species representing vertebrates (acute, dietary, reproduction exposure)

For the assessment of risks, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with metiram. For multiple applications, the cumulative application rates were calculated taking into consideration the dissipation half-life of metiram complex in soil (135 days) and on foliage (10 days).

A risk assessment of ETU to terrestrial organisms was based on an evaluation of toxicity data to terrestrial mammals (acute, dietary and reproduction exposure). Mammalian toxicity data for ETU is summarized in Table 2 (Appendix IX). However, the PMRA chose to conduct a worse-case risk assessment for ETU using the use pattern of mancozeb because it has the broadest use pattern of the EDBC fungicides and the highest application rate (apples at 4800 g mancozeb/ha × 6 applications at 7 day intervals) thus providing an all-inclusive view of risks posed by ETU.

Risk assessment of ETU to terrestrial organisms is not covered in this document.

Terrestrial Invertebrates
The screening level risk assessment of metiram complex indicated that the level of concern for earthworms and bees was not exceeded for any of the application rates (Table 3, Appendix IX).

Although the laboratory toxicity tests for *Pardosa* sp. demonstrated little toxicity (5%) and the screening level risk assessment indicated that the level of concern was only slightly exceeded (RQ = <3.3 - <3.8), the limit dose used in the toxicity tests was significantly lower than the cumulative application rate. Consequently, potential adverse effects on terrestrial invertebrates at the current registered application rates cannot be excluded.

Adverse effects on the predatory mite, *Typhlodromus pyri*, were evident from the laboratory toxicity data. Furthermore, field studies investigating the impact of metiram complex on *T.pyri* on grapevines in Germany indicated that 40-91% reductions in their populations were observed relative to control sites four weeks after the last of 6 to 8 applications at rates up to 2.5 kg a.i./ha. The current rate for one application in Canada (4.8 kg a.i./ha) on apple orchard is higher than the cumulative rate used in the submitted field studies; therefore, adverse effects on non-target predators and parasites are expected under Canadian use conditions. As a result, a statement is required on metiram product labels.

Terrestrial Plants

No data was submitted by the registrant regarding the toxicity of metiram complex to non-target terrestrial vascular plants, nor were any relevant studies found in the open literature. Either Tier I studies on terrestrial plants conducted at rates equivalent to the maximum cumulative application rate or suitable science rationale justifying why the studies are not needed are required. However, if phyto-toxicity is shown in Tier I data, Tier II data may be required.

Terrestrial Vertebrates

Exposure is dependent on the body weight of the organism and the amount and type of food consumed. In the screening level assessment a set of generic body weights was used for birds (20, 100, 1000g) and small wild mammals (15, 35, 1000 g) to represent a range of bird and small wild mammal species with the respective food ingestion rates, for each body weight. Although diets of animals can be highly variable, for the screening level assessment, relevant food categories for each size group consisting of 100% of a particular dietary item were used. These items included the most conservative estimated residue concentrations for plants, grains/seeds, insects, and fruits. A 100% diet of plants for the smallest sizes of birds and mammals was not included as this was considered unrealistic as unrealistically high amounts of leafy plant material or grass would not meet their energy requirements.

Birds

The results of the screening level risk assessment to birds are presented in Table 4 (Appendix IX). The assessment shows that following application of metiram at the maximum cumulative application rate on apple orchards (4800 g a.i./ha × 4 x7 days interval), the risk quotients (RQ) for all bird sizes and food preference categories exceeded the level of concern (LOC) for acute effects (RQ = 1.96 to 2.5). For the chronic effects on all bird sizes and food preference categories, the risk quotients exceeded the LOC by a much larger margin (RQ = 201.2 – 257.8). (Table 4, Appendix IX).

Given the conservative assumptions taken in the screening level risk assessment, the risks to birds were further characterized using the mean residue values on terrestrial food sources (Table 6, Appendix IX). In addition, for risk quotients exceeding the LOC, two additional parameters were calculated to assess the relevance of the determined risk: 1) the percent daily diet required to reach the LOC (calculated as 1/RQ × 100), and 2) the number of days that residues remain on food items above the LOC; (calculations based 10 d foliar half-life).

The refined risk assessment is summarized in Table 6, Appendix IX. The risk quotient exceeded the level of concern for acute effects only in 20g insectivores and 1 kg leafy foliage herbivores feeding on a site with the highest cumulative metiram application rate (RQ = 1.3 – 1.4). Although an acute risk is identified, the PMRA concluded that acute risks to birds would be minimal. The level of concern for dietary effects was not exceeded (LOC < 1).

At the current registered maximum cumulative application rate on apples, the risk quotients exceeded the LOC for chronic effects for all bird sizes and food preference categories (Table 6, Appendix IX). At the current minimum cumulative application rate, the LOC for chronic effects is exceeded on the treated fields for all bird sizes and feeding guilds. Outside the treated field, the level of concern is exceeded for 20g insectivores, 100 g insectivores and 1 kg herbivores feeding on short grass and leafy foliage. The percent diet required to reach the LOC at the current maximum application was found to be relatively low (for example, 0.9 – 14% on field; 1-19% off-field) based on assumed foliar half-life of 10 days and multiple applications. The residue levels on food items were found to remain above the LOC from the second day of application for as long as 137 days (Table 7, Appendix IX).

Mammals

The screening level risk assessment showed that the risk quotient exceeded LOC for acute effects (RQ = 1 - 1.94) on the treated fields. The risk quotients for chronic effects for all generic weights and feeding guilds of small wild mammals exceeded the LOC by a much larger margin (RQ = 172 - 539). The screening level risk assessment for small wild mammals is presented in (Table 4, Appendix IX).

The refined risk assessment for small wild mammals is presented in Table 6, Appendix IX. On refinement using the mean residue concentrations on food items, the level of concern for acute effects was not exceeded both on-field and off-field. The level of concern for chronic effects was however exceeded for all generic weights and feeding guilds of small wild mammals following the application at the maximum cumulative (RQ = 9.6 – 179.6 on-field; 7.1 – 132.9 off-field) or minimum application rates (RQ = 2.6 – 48.8 on field). At the minimum application rate, the level of concern for chronic effects outside the treated field was exceeded for 15 g insectivores (RQ = 1.6); 35 g insectivores and herbivores feeding on short grass, forage crops and leafy foliage (RQ = 1.4 – 2.9); and 1kg herbivores feeding on short grass, forage crops and leafy foliage (RQ = 1.4 – 2.9).

At the current registered application rates, small wild mammals feeding at the site of metiram application would need to consume 2-38% of their diet on contaminated food in order to reach the level of concern (Table 6, Appendix IX). The residue levels on food items were found to remain above the LOC for as long as 108 days (Table 7, Appendix IX).

Overall Conclusions for Terrestrial Vertebrate Risk Assessment

Metiram can be applied 4 times per season every 7 days from pre-bloom through the foliar stages of apples. The timing of pre-bloom application (first application of the season) varies across Canada but, generally begins late March to early April which coincides with the start of breeding activities of most avian and mammalian species. Many species of birds visit apple orchards for food and shelter, including nesting and breeding. In addition, small wild mammals have been known to inhabit apple orchards as well as visit orchards as a food source. Given that the timing of application for metiram coincides with the timing of breeding activities, potential for adverse reproductive risks exists for birds and small wild mammals that frequent apple orchards in which metiram is applied.

Further characterization of the risks emanating from the current registered use of metiram on apples by use of estimated daily exposure (mg a.i/kg bw) on various avian and mammalian food items indicates that both birds and small wild mammals would be prone to reproductive risks beginning on day 1 after application and continuing throughout the apple production period or for more than 72 days (Table 6, Appendix IX).

In addition to the use on apples, metiram is also registered for use on grapes, potatoes, beets, carrots, tomatoes, asparagus and celery. Each of these groupings represents a unique use pattern based on rates of application, number of applications and minimum interval between applications. The conclusions drawn for these other crop groupings are similar to the results using apples (Table 7, Appendix IX).

Although there are no reported incidents on birds and mammals from the use of metiram, it is not unusual that chronic effects on wildlife from the use of metiram would go unnoticed in the field. Overall, the refined risk assessment shows that use of metiram at the current registered rates poses potential reproductive risks to birds and small wild mammals.

4.2.2 Risks to Aquatic Organisms

The PMRA assessed the risks of metiram complex and its transformation product ETU to aquatic organisms. Although ETU was found to be toxic to aquatic organisms, its toxicity was found to be less than that of the metiram complex. Hence, the toxicity endpoints from exposure to metiram complex were the main drivers of the current aquatic risk assessment.

The risk assessment of metiram complex to aquatic organisms was based upon evaluation of toxicity data for the following (Table 5, Appendix IX):

- one freshwater invertebrate species (acute and chronic exposure)
- one freshwater fish specie (acute exposure)
- one freshwater alga

Screening Level Assessment

Table 5 (Appendix IX) summarizes the screening level risk assessment of metiram complex for aquatic organisms. The level of concern for acute effects was exceeded for freshwater invertebrates, freshwater fish, freshwater green algae and amphibians (based on surrogate data from fish studies) for both the maximum (RQ = 6 - 161.8) and the minimum (RQ = 1.2 – 31.2) cumulative application rates. The level of concern for chronic effects to aquatic organisms was exceeded for freshwater invertebrates (the only data available) for both the maximum and minimum cumulative application rates (RQ = 17.8 - 92.2). (Table 5, Appendix IX)

Refined Assessment

A refined risk assessment (Table 8, Appendix IX) was conducted for non-target aquatic organisms taking into consideration the concentrations of metiram complex that could be present in aquatic habitats 1 metre downwind from the application equipment as a result of spray drift or from run-off.

For EECs estimated for ground boom applications on potatoes and sugar beets, the LOC for acute effects was exceeded for freshwater fish, green algae and amphibians (RQ = 1.63 - 8.7). The LOC for chronic effects was exceeded for freshwater invertebrates (RQ = 4.6 – 19) (Table 8, Appendix IX).

For EECs estimated following aerial applications on potatoes, the LOC for acute effects was exceeded for freshwater invertebrates, fish, green algae and amphibians (RQ = 1.2 to 33.3). The LOC for chronic effects was exceeded for freshwater invertebrates only (RQ = 19) (Table 8, Appendix IX).

Following airblast applications on apples and grapes, estimated EECs resulted in LOC for acute effects being exceeded for freshwater invertebrates, fish, green algae and amphibians respectively (RQ = 4.4 - 119.7), (Table 8, Appendix IX). The LOC for chronic effects was exceeded for freshwater invertebrates (RQ = 17.3 - 68.2) (Table 8, Appendix IX).

Estimated environmental concentrations (EECs) of metiram complex from runoff into a receiving water body were estimated using the PRZM/EXAMS models. The PRZM/EXAMS models simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. For the Level 1 assessment, two bodies of water were considered:

a) 1 ha wetland with an average depth of 0.8 m and a drainage area of 10 ha (representing a permanent water body) and
b) 1 ha wetland with an average depth of 0.15m and a drainage area of 10 ha (representing a temporal water body).

Ten standard scenarios were used to represent the different use patterns for apples and potatoes in the different regions of Canada. Two to three initial application dates were modelled for each scenario; dates ranged between March and April for the apple use pattern and between May and June for the potato use pattern. Deposition from spray drift was not included in the simulations, so these EECs are for the portion of the pesticide that enters the water body via runoff only. The model was run for 50 years for all scenarios. For each year of the simulation, PRZM/EXAMS calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the daily concentrations over five time periods (96 hours, 21days, 60 days, 90 days, and 1 year). The 90th percentiles over each averaging period are reported as the EECs for that period. The EECs with the appropriate time periods were used to calculate the risk quotients, for example 96-hour for acute endpoints and 21-day for chronic endpoints. Table 8 (Appendix IX) summarizes the refined risk assessment to aquatic organisms from metiram runoff.

The acute level of concern for freshwater fish, algae and amphibians is exceeded (RQ = 1.9 to 5.6) in the apple scenario and for freshwater invertebrates, fish, algae and amphibians (RQ =1.7 to 24.1) in the potato scenario respectively.

The chronic level of concern is exceeded for freshwater invertebrates (RQ = 5.2 to 23.2) in apple and potato scenarios, respectively. Aquatic organisms would, therefore, be at potential adverse effects from residues of metiram complex in runoff following the current apple and potatoes use-pattern scenarios in Canada.

4.2.3 Conclusion on Environmental Risks

A re-evaluation of metiram was conducted by the USEPA (USEPA, 2005). Overall, the USEPA concluded that there were some exceedances of the chronic levels of concern, especially from metiram applications to apples and potatoes. Therefore to be more protective of species that may be exposed on a chronic basis, the USEPA, recommended additional label changes to reduce potential risks. These changes include reducing the maximum application rates to apples and the maximum number of applications to apples and potatoes.

The PMRA recognizes that the American use pattern for metiram encompasses the Canadian use pattern, and proposes that risk-reduction measures including reduction in application rates recommended by the USEPA should be applied to Canadian metiram products.

A refined risk assessment was carried out with the USEPA recommended rates. Table 9, Appendix IX, compares the risk quotients and summarizes the percentage risk reduction from the use of the recommended rates for both terrestrial and aquatic organisms. Although the USEPA recommended rates do not eliminate the risks, they reduce the risks by up to 25 – 30%. The refined risk assessment indicates that at the application of the USEPA recommended rates, the risk quotients would still remain relatively high (RQ =3.5 to 135.2 on-field and 1.6 to 100 off-field) for use patterns without aerial application.

The following is recommended:

- Reduction of the apple pre-bloom maximum application rate to 4035 g a.i./ha from 4800 g a.i./ha;
- Reduction in the maximum number of applications for apples from 4 to 3 per year;
- Reduction in the maximum number of applications for potatoes from 10 to 6 per year;
- Aquatic spray buffer zones were calculated by the PMRA to minimize spray drift to non-target aquatic species during aerial application. The PMRA based the spray buffer zone calculations on limited aquatic toxicity data. Additional data are requested to confirm that the proposed aquatic spray buffer zones adequately protect sensitive aquatic habitats;
- Data on the toxicity of metiram to non-target terrestrial vascular plants are required to calculate spray buffer zone distances for the protection of sensitive terrestrial habitats.

4.2.4 Incident Reports, or Special Use Pattern

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS). If information on environmental incidents is available from other governments (such as OECD countries) this information is also taken into consideration. Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act* can be found at http://laws-lois.justice.gc.ca/eng/regulations/SOR-2006-260/FullText.html.

No environmental incident reports were found for metiram in either the Canadian pesticide incident report system or the USEPA Ecological Incident Information System (EIIS). Even though metiram, on an acute basis, appears to pose a low risk to terrestrial animals and plants, the chronic LOC's to terrestrial animals (birds and mammals) are exceeded for all metiram use patterns. Generally, incident reports submitted to both the USEPA and the PMRA deal with field mortality of wildlife. Chronic/reproductive problems that affect wildlife from the use of metiram would be expected to be largely unnoticed in the field and thus incident reports, as a result of chronic expsoure, would not be expected.

There were no incident reports concerning ETU. Since ETU is a transformation product that is formed from the EBDCs, it is unlikely that incident reports for ETU would be received. Any incident reports would probably be most likely for one of the parent EBDCs, not specifically for ETU.

5.0 Value

5.1 Commercial Class Uses for Which Information on the Value of Metiram is Sought

Appendix III lists those uses of metiram that the registrant continues to support but that have raised risk concerns as a result of this re-evaluation. The PMRA welcomes feedback on the availability and extent of use of the chemical alternatives to metiram for the sites and diseases listed in Appendix III and further information regarding the availability, effectiveness and extent of use of non-chemical pest management practices for any of the registered uses of metiram. This information will allow the PMRA to refine sustainable pest management options for the listed site-pest combinations.

5.2 Value of Metiram

5.2.1 Uses

Metiram is registered in Canada for the control of a number of fungal diseases on several field and orchard crops including some of the most destructive plant diseases: downy mildew (*Plasmopara viticola*) on grapes, scab (*Venturia inaequalis*) on apples, early blight (*Alternaria solani*) and late blight (*Phytophthora infestans*) on tomato and potato, and rust on asparagus. It has also been reported to be used as a potato seed piece treatment for the control of seed borne common scab and Fusarium seed piece decay. Of these, the most important uses of metiram, where a large proportion of the crop is treated, include foliar treatments to control scab on apples, and early and late blight on potato.

5.2.2 Apple Scab

Apple scab (*Venturia inaequalis*) is the most serious fungal disease of apples in Canada. It damages foliage, blossoms and fruit resulting in up to 100% loss in yield (Solymar and Appleby, 2005). A wide variety of fungicides are registered for managing apple scab (Canadian Horticultural Council, 2010). Of these, the most viable alternatives to metiram for the control of apple scab are: mancozeb, captan, trifloxystrobin, myclobutanil and kresoxim-methyl. In an ideal apple scab management program in Ontario, for example, usually up to a four applications of an EBDC fungicide such as metiram or mancozeb are made early in the season followed by a maximum of two applications of a systemic fungicide such as trifloxystrobin, myclobutanil, or kresoxim methyl and a maximum of four applications of captan (a muti-site fungicide) in the latter part of the season generally after petal fall (Carter *et al.*, 2011). In apple disease management programs in Canada, almost an equal percentage of crops are treated with each of metiram and mancozeb.

The development of resistance by the apple scab pathogen to most of the systemic fungicides has been recorded (Agriculture and Agri-Food Canada, 2004; Solymar and Appleby, 2005; British Columbia Ministry of Agriculture and Lands, 2008). Thus, metiram is an important chemical for apple scab control and resistance management in IPM programs for apples in Canada due to its protective activity and its multi-site mode of action making it less prone to the development of resistance.

5.2.3 Early and late blights on potatoes and tomatoes

Early and late blights (*Alternaria solani* and *Phytophthora infestans*, respectively) are the most common diseases of potatoes and tomatoes in Canada. If not controlled, late blight can be a very devastating disease on these crops. A large number of fungicides belonging to several different resistance management groups are registered in Canada for the control of these diseases (Agriculture and Agri-Food Canada, 2005). Most fungicides that are used to control late blight also control early blight. The most viable alternatives to metiram for the control of late blight on potatoes are: mancozeb, chlorothalonil, azoxystrobin, mandipropamid, cymoxanil, cyazofamid, metalaxyl-m, fenamidone and fluazinam. The development of resistance to some of these systemic fungicides (for example, azoxystrobin and metalaxyl-m) in some isolates of early and late blight pathogens has been reported in Canada (Peters *et al.*, 2008). The use of metiram for the control of potato diseases is several times less than the use of mancozeb.

Early and late blights on potatoes and tomatoes can be effectively controlled by implementing an IPM program. Metiram is important as a protectant and rotational fungicide in an IPM program for the control of these diseases on potatoes and tomatoes in Canada. Due to the development of resistance to some of the registered alternative fungicides, growers must now rely on a more stringent program of repeated application of protectant fungicides (Agriculture and Agri-Food Canada, 2005). This emphasizes the importance of the currently registered protectant fungicides with multi-site mode of action such as metiram.

5.2.4 Asparagus rust

Asparagus rust caused by *Puccinia asparagi*, is an important disease of asparagus. The fungus develops in asparagus fern and drains the plant of vital nutrients. The foliage then dries out and falls prematurely. Metiram is the only EBDC fungicide registered in Canada for control of asparagus rust on asparagus since the expiration of zineb as of 31 December 2010. Zineb was recommended for this use in Ontario prior to its expiration (Wukasch, 2009). The other alternatives to metiram for the control of rust on asparagus are: propiconazole, myclobutanil and chlorothalonil. Propiconazole and myclobutanil are single-site systemic fungicides and chlorothalonil is a multi-site contact fungicide.

5.2.5 Resistance Management

Metiram has been used in Canada for a long period of time on field and orchard crops. The development of resistance to this fungicide in plant pathogens has not been reported to date. Metiram is effective as a contact fungicide and has a multi-site mode of action and, as such, fungal pathogens are not prone to develop resistance to it. Due to this property, it is an important tool for sustainable pest management and contributes to resistance management in an integrated pest management (IPM) program where it is used as a rotational fungicide or as a tank-mix partner with other single-site modes of action fungicides which are at high risk for resistance development. Thus metiram helps to prolong the useful life of these single-site modes of action fungicides registered for similar uses.

Because of its multi-site mode of action, compatibility with other products, redistribution properties, and lower cost per treatment, metiram has become one of the most important chemicals in IPM programs in apples and potatoes in Canada and a large proportion of these crops are treated every year with it. Consequently, metiram plays an important role in apple and potato production in Canada.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and /or sediment, bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*).

During the review process, metiram and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Metiram does not meet Track 1 criteria, and is not considered a Track 1 substance. See Table 10 of Appendix IX for comparison with Track 1 criteria.

- Metiram forms the following main transformation products that do not meet all Track 1 criteria.
    - Ethylene thiourea (ETU), Ethylenebis (isothiocyanate) sulfide (EBIS), ethylene urea (EU), Carbimid, 2,3,7,8-tetrahydrodiimidazo[2,1-b:1,2-e][1,3,5]thiadiazine -5-thione (TDIT), Hydantoin, methylthiourea.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[7]. The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies and regulations including DIR99-03 and DIR2006-02[9], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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[6] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

[7] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[8] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[9] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

- Technical grade metiram and the end-use product Polyram DF Water Dispersible granular fungicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- There are no formulants or contaminants of concern associated with ETU because it is not manufactured as a technical or used as an end-use product.

7.0 Summary

7.1 Human Health and Safety

The toxicological database for metiram contains both published and unpublished studies that were considered in the toxicology assessment. Although a rabbit developmental toxicity and a rat reproductive toxicity study were available, there were limitations in both studies. The database lacked an acute neurotoxicity study and a developmental neurotoxicity study. Based on available data, the most sensitive endpoints were effects on the thyroid and nervous system. In pregnant rats, increased postimplantation loss was noted at maternally toxic doses. Although the weight of evidence indicates that metiram is not genotoxic, cancer concerns exists for metiram based on ethylene thiourea (ETU), a metabolite of metiram and all EBDCs.

ETU is a metabolite of the EBDC group of fungicides, which includes the related active ingredients mancozeb, maneb, metiram, zineb and nabam. Currently, mancozeb, metiram and nabam are registered for use in Canada. The toxicological database for ETU contains numerous published and unpublished studies that were considered in the toxicology assessment. For the purpose of this re-evaluation, the reproduction studies were considered supplemental and the database was lacking a developmental neurotoxicity study with a comparative (adult vs young) thyroid assay. The primary targets are the thyroid, liver and developmental toxicity. ETU has been shown to cause thyroid cancer in both mice and rats and liver cancer in female mice. This carcinogenic risk was addressed with a q_1^* (non-threshold) approach.

7.1.1 Occupational Risk

For mixer/loader/applicators, the calculated MOEs exceed the target MOE provided that additional PPE (such as coveralls over a single layer and gloves, and respirators during application for some crops), engineering controls (closed mixing and loading, and closed cab for some crops), and restrictions on area treated per day (apples, sugar beets, and potatoes only) are implemented.

For workers entering treated agricultural crops, acceptable MOEs were not achieved for the vast majority of postapplication activities including hand harvesting, scouting/irrigation, and thinning. Except for a few minor contact activities (such as hand weeding of asparagus, and thinning and hand weeding of sugar beets), depending on the degree of foliar contact, acceptable MOEs were not achieved until 27 to >175 days postapplication. These restricted entry intervals are not considered practical.

7.1.2 Dietary Risk from Food

Metiram
The acute exposure risk estimate for females aged 13 to 49 years did not exceed the ARfD and is not of concern. However the chronic exposure risk estimate exceeds the ADI and is of concern.

ETU
The acute and chronic risk estimates associated with exposure to ETU from food is not of concern for all population subgroups. However the cancer risk of 9×10^{-6} from food alone exceeds the threshold of 1×10^{-6}, and is of concern.

7.1.3 Aggregate Risk from Food and Water

Metiram is not expected to be present in drinking water. Therefore, the aggregate risk assessment from food and drinking water was conducted only for ETU. The acute deterministic risk estimate is less than the acute reference dose and is not of concern. The chronic risk estimate exceeds the ADI by 7% but is not considered to be of concern due to the use of some conservative inputs.

The aggregate cancer risk estimate of 12×10^{-6} for ETU is of concern. Non-occupational exposures (for example, Pick-your-own facilities and bystander exposure from fruit tree applications) were not included in the aggregate assessment since cancer risk for ETU from aggeregate food and water exposure alone is of concern.

7.1.4 Cumulative Risk

Exposure to ETU in food and drinking water may also occur from the use of mancozeb or any other EBDC fungicides. Presently, mancozeb is the only other EBDC fungicide with registered food uses in Canada while nabam is registered in Canada only for industrial uses.

Exposure to ETU in the environment or in occupational settings may occur from non-pesticidal sources of ETU. These sources are regulated separately (*Canadian Environmental Protection Act, 1999*) from the exposure derived from the pesticidal use.

As the aggregate exposure from food and water to metiram alone is of concern, a combined/cumulative risk assessment was not conducted at this time. It is acknowledged that the drinking water exposure estimates does represent the total exposure from ETU from all pesticidal sources (mancozeb and metiram). However, as the aggregate risk for metiram and mancozeb are estimated independently, this approach does not over-estimate the risk.

Mitigation options for the dietary exposure risk include a revised use pattern for agricultural uses. The registrant has an option to propose this during consultation period.

As an additional measure to mitigate potential aggregate risk from ETU exposure (from all EBDC pesticides and sources), the following label statement is proposed to be added to the labels of mancozeb and metiram during the phase-out of metiram to limit applications of these actives so that the total quantity of active does not exceed the specified maximum seasonal quantity for either mancozeb or metiram.

"If more than one product containing an EBDC-active ingredient (mancozeb or metiram) is used on a crop during the same growing season, the total quantity of all such EBDC products used must not exceed any one of the specified individual EBDC product maximum seasonal quantity of active ingredient allowed per hectare."

7.2 Environmental Risk

The use of metiram at the current registered application rates and use patterns, would pose potential risk to terrestrial and aquatic organisms, including beneficial arthropods, birds and small wild mammals, freshwater invertebrates, fish, algae and amphibians.

Effects in the terrestrial ecosystem are often difficult to mitigate due to the occurrence of non-target species in treated areas. Risk to beneficial insects living in habitats adjacent to the application site may be reduced by minimizing spray drift. Appropriate environmental hazard statements are included on product labels to educate users to help mitigate the risk to beneficial insects. For other terrestrial organisms such as birds and mammals, mitigation options are limited and include decreased application rates, number and/or frequencies of application, depending on the potential impact on efficacy. Nevertheless, even with a reduction in rates and times of application, potential reproductive risks to birds and mammals are still identified.

In the aquatic environment, metiram, at the current registered application rate poses risks to aquatic organisms. A risk assessment based on spray drift input to the aquatic environment and from runoff indicated that metiram would pose a risk to aquatic organisms. The risk from spray drift can be adequately mitigated through the observance of spray buffer zones.

7.3 Value

Metiram is registered to control a broad range of economically important fungal diseases on a number of field and orchard crops. The most important uses of metiram include foliar treatments to control scab on apples, early and late blight on potatoes and rust on asparagus. Metiram has a multi-site mode of action and, thus, is an important tool for resistance management in IPM programs for most of the registered site-pest combinations.

8.0 Proposed Regulatory Decision

The PMRA is proposing the phase-out of all uses of metiram in Canada since they do not meet Health Canada's current standards for human health and the environment protection. During the transition to phase out, additional measures are proposed for these uses to reduce potential human health and environment risks. Additional data are identified and may help refine the risk assessments for metiram. During the consultation period, the registrant may consider submission of these data or propose changes to the use pattern that could be used to address risk concerns.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

8.1.1.1 Toxicological Information

As an additional measure during the phase out of metiram, the following warning statements should appear on the label of the technical product:

"Potential Skin Sensitizer":

The EBDC fungicides may cause irritation of the skin, respiratory tract and eyes.

8.1.1.2 Residue Definition and MRL for Risk Assessment and Enforcement – Pending Phase-Out Decision

As chemical specific enforcement methods for the EBDC fungicides, including metiram, are not currently available, the current residue definition established under the *Pest Control Products Act* is "manganese and zinc ethylenebis(dithiocarbamate) (polymeric)", which is common for all EBDC pesticides. PMRA is proposing to revise the residue definition for metiram, to residues of "metiram expressed as carbon disulphide (CS_2)". These proposed changes are pending the availability of acceptable field trial data at the Canadian GAP.

The residue definition of ETU for risk assessment and MRLs is "ethylene thiourea".

8.1.1.3 Maximum Residue Limits for Metiram in Food

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to update Canadian maximum residue limits and to remove MRLs that are no longer supported. The PMRA recognizes, however, that interested parties may want to retain an MRL in the absence of a Canadian registration to allow legal importation of treated commodities into Canada. The PMRA requires similar chemistry and toxicology data for such import MRLs as those required to support Canadian food use registrations. In addition, the PMRA requires residue data that are representative of use conditions in exporting countries, in the same manner that representative residue data are required to support domestic use of the pesticide. These requirements are necessary so that the PMRA may determine whether the requested MRLs are needed and to ensure they would not result in unacceptable health risks.

Common MRLs for domestic and import uses of metiram as well as EBDCs have been established on registered agricultural commodities and published in Health Canada's List of MRLs Regulated under the *Pest Control Poducts Act* on the Maximum Residue Limits for Pesticides webpage. Currently, EBDC fungicides including mancozeb and metiram are registered under the *Pest Control Products Act.* MRLs of EBDC fungicides resulting from their use in Canada and in other countries are established at: 7 parts per million (ppm) in apples, broccoli, Brussels sprouts, cabbages, cauliflower, eggplants, grapes, lettuce, mushrooms, onions (green), pears and peppers, 5 ppm in celery and 4 ppm in cucumbers and tomatoes.

By virtue of subsection B.15.002(1) of the *Food and Drug Regulations*, the MRL for other foods is 0.1 ppm when no specific MRL is established for a pest control. This requires that residues do not exceed 0.1 ppm, which is considered a general MRL for enforcement purposes. However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*. If and when the general MRL is revoked, a transition strategy will be established to allow permanent MRLs to be set for specific commodities.

As metiram belongs to the EBDC group of fungicides, amendments to the MRLs will need to take into consideration the regulatory proposals for all EBDC compounds.

8.1.1.4 Maximum Residue Limits for ETU in Food

There are no specific MRLs established for ETU. However, residues in food from all sources are regulated separately under the B.01.046 and B.01.047 section of the *Food and Drug Regulations*. No amendment of this MRL is proposed.

8.1.1.5 Proposed Additional Measures for Mixer, Loader and Applicator Exposure and Post-Application Exposure During Phase-Out

As an additional measure during the phase out of metiram, the following regulatory actions are required.

Water Dispersible Granule in Water Soluble Packaging (WSP):

The currently registered metiram product listed as a water dispersible granule must be in water soluble packaging. The registrant is required to include directions and precautionary statements for water soluble packaging on all end-use product labels.

Use Precautions:

There may be potential for exposure to bystanders from drift following pesticide application to agricultural areas. In the interest of promoting best management practices and to minimize human exposure from spray drift or from spray residues resulting from drift, the following label statement is required:

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

Engineering Controls and Personal Protective Equipment:

Statements must be amended (or added) to include the following directions to the appropriate labels in order to mitigate the risk of exposure to metiram:

"Wear coveralls over long pants, long-sleeved shirts and chemical-resistant gloves during mixing/loading, application, clean-up, and repair. Chemical-resistant gloves are not required while operating groundboom sprayers. Aerial applicators must wear long pants, long sleeved shirts, and chemical-resistant gloves."

For the following use scenarios, additional PPE, restrictions and/or engineering controls must also be included on all labels:

Apples
Airblast Equipment

- Limit the amount of active ingredient handled per day to 45 kg per person (approx. 9.5 ha at 4.8 kg ai/ha).
- During airblast application use a closed cab that provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system). The closed cab must have a chemical resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab.

Asparagus, Celery, Tomato, Carrot
Groundboom Equipment

- During groundboom application, applicators must wear either a respirator with a NIOSH/MSHA/BHSE approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH/MSHA/BHSE approved canister approved for pesticides.

Grapes
Airblast Equipment

- During airblast application use a closed cab that provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system). The closed cab must have a chemical resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab.

Sugar Beets and Potatoes
Groundboom Equipment

- Limit the amount of active ingredient handled per day to 125 kg per person (approx. 70 ha at 1.8 kg ai/ha).
- During groundboom application, applicators must wear either a respirator with a NIOSH/MSHA/BHSE approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH/MSHA/BHSE approved canister approved for pesticides.

Potatoes
Aerial Equipment

- Limit the amount of active ingredient handled per day to 195 kg per person (approx. 110 ha at 1.8 kg ai/ha).

Restricted Entry Intervals (REI):

The restricted entry intervals needed to reach the target MOE are presented below. As these REIs are not practical, consultation is required to determine interim REIs.

Table 8.1.1.4: Recommended Restricted Entry Intervals

Crop	Activity	Restricted Entry Interval (days)
Apples	Thinning	>170
	Hand Harvesting	146
	Hand Line Irrigation	132
	Pruning/Scouting	98
	Hand Weeding	27
Asparagus	Scouting/Irrigation	71
	Hand Weeding	12 hrs
Celery	Hand Harvest	142
	Scouting/Irrigation	119
	Hand Weeding	71
Tomato	Hand Harvest	101
	Scouting/Irrigation	86
	Hand Weeding	71
Carrot	Hand Harvest	125
	Scouting/Irrigation	32
Sugar Beets	Scouting/Irrigation	79
	Thinning/Hand Weeding	12 hrs
Potatoes	Scouting/Irrigation	133
	Thinning/Hand Weeding	62
Grapes	Cane Turning/Girdling	>175
	Hand Harvest	165
	Hand Line Irrigation	75
	Scouting/Hand Weeding	55

8.1.1.6 Proposed Mitigation for Dietary Exposure

Mitigation options for the dietary exposure risk include a revised use pattern for agricultural uses. The registrant has an option to propose this during the consultation period.

As an additional measure to mitigate potential aggregate risk from ETU exposure (from all EBDC pesticides and sources), the following label statement is proposed to be added to the labels of mancozeb and metiram during the phase-out of metiram to limit applications of these actives so that the total quantity of active does not exceed the specified maximum seasonal quantity for either mancozeb or metiram.

"If more than one product containing an EBDC-active ingredient (mancozeb or metiram) is used on a crop during the same growing season, the total quantity of all such EBDC products used must not exceed any one of the specified individual EBDC product maximum seasonal quantity of active ingredient allowed per hectare."

8.1.2 Proposed Regulatory Action Related to Environment

To reduce the effects of metiram in the environment, mitigation in the form of precautionary label statements, reduction in application rates and spray buffer zones are required.

As an additional measure during the phase out of metiram, environmental mitigation statements are listed below:

Add an **ENVIRONMENTAL HAZARfDS** section to the label with the following statements:

- TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.
- TOXIC to small wild mammals.
- TOXIC to birds.
- TOXIC to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland.
- To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.
- Avoid application when heavy rain is forecast.
- Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

- The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable (for example, sandy soil) and/or the depth to the water table is shallow.

Add to GENERAL DIRECTIONS FOR USE after the MIXING INSTRUCTIONS:

- As this pesticide is not registered for the control of pests in aquatic systems, **DO NOT** use to control aquatic pests.

- **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

Buffer Zone Related Label Statements Required:

Add to ENVIRONMENTAL HAZARfDS:

TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer, and spot treatment.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands and estuarine/marine habitats).

Method of application	Crop		Buffer Zones (metres) Required for the Protection of Aquatic Habitat of Depths:	
			Less than 1 m	Greater than 1 m
Field sprayer*	Sugar beets, asparagus, carrot, celery, tomato, potato		3	2
Airblast	Grape	Early growth stage	20	10
		Late growth stage	10	4
	Apple	Early growth stage	35	25
		Late growth stage	25	15
Aerial	Potato	Fixed wing	90	25
		Rotary wing	65	20

*For field sprayer application, buffer zones can be reduced with the use of drift reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy, the labelled buffer zone can be reduced by 30%.

8.2 Additional Identified Data

During the consultation period, the registrant may consider submission of the following data or propose changes to the use pattern that could be used to address risk concerns:

8.2.1 Data Related to Toxicology

Metiram

DACO 4.5.1 Two-generation Reproductive Toxicity Study in Rat
DACO 4.5.12 Acute Neurotoxicity Study
DACO 4.5.14 Developmental Neurotoxicity Study
DACO 4.5.3 Rabbit Developmental Toxicity Study

ETU

DACO 4.5.1	Two-generation reproductive toxicity study in rat
DACO 4.5.14	Developmental Neurotoxicity Study, with comparative thyroid assay (adult/young)

Or

DACO 4.5.1 and 4.5.14 can be addressed by submitting an Extended One-Generation Reproductive Study with both reproductive and developmental neurotoxicity cohorts. A comparative thyroid assay can also be addressed within these cohorts.

8.2.3 Data Related to Occupational Exposure

The following studies may help refine the occupational assessment for metiram:

DACO 5.2	Use Description/Scenario (all uses) – This includes information which fully describes the use of the product and human activity associated with its use. Specifically, information on the average number of days per year metiram is used, and the average number of days per year each postapplication activity occurs, and whether postapplication activities coincide with metiram application.
DACO 5.9	Dislodgeable Foliar Residue Data – Dislodgeable foliar residue data representative of several of the registered crops and Canadian climatic regions, measuring both metiram and ETU.
DACO 5.14	Other Studies/Data/Reports – Tank mix stability data that quantifies the amount of ETU formed in metiram formulations.

It should be noted that even if all of the above-noted data is submitted, the refinements in the exposure estimates might not be sufficient to reach target MOEs for the postapplication assessment.

8.2.4 Data Related to Food Residue Chemistry

DACO 7.4.1	Supervised residue field trials performed in Canadian regions according to Canadian GAP for asparagus, carrot, celery, grapes, sugar beets and tomatoes based on the registrant support for the continued registration of the respective commodity. Data should be provided for metiram and ETU residues.
DACO 8.6	Additional data is required to characterize the potential exposure to ETU through drinking water. Based on the identified human health risk coming from the ETU residues potentially present in the water, confirmatory water data is required to address the determined exposure risk.

8.2.5 Data Related to Environment

The PMRA did not have any information on the toxicity of ETU to birds. Considering that the risk assessment shows that ETU may pose a risk to mammals, avian toxicity data for ETU is required.

ETU studies:

DACO 9.6.1	Wild Birds Summary
DACO 9.6.2	Acute Studies
DACO 9.6.2.1	Oral (LD50) Bobwhite Quail
	or
DACO 9.6.2.2	Oral (LD50) Mallard Duck
DACO 9.6.3.1	Avian Reproduction Bobwhite Quail
	or
DACO 9.6.3.2	Avian Reproduction Mallard Duck

8.2.6 Data Related to Value

- Quantitative and/or qualitative data on the economic and social importance of metiram to specific industries; and
- Feedback on the viability of alternative chemical and non-chemical pest management practices for the site and pest combinations.
- Other benefits and information on the contribution of metiram to sustainable pest management and agriculture in Canada.

List of Abbreviations

a.i.	active ingredient
AAFC	Agriculture and Agri-Food Canada
AChE	acetylcholinesterase
ADI	acceptable daily intake
ARfD	acute reference dose
atm	atmosphere
BCF	Bioconcentration Factor
BChE	brain acetylcholinesterase
BUN	blood urea nitrogen
bw	body weight
Cal DPR	California Department of Pesticide Registration
CAS	chemical abstracts service
CFIA	Canadian Food Inspection Agency
ChE	cholinesterase
CI	confidence interval
cm	centimetre(s)
CT	crop treated
DEEM®	Dietary Exposure Evaluation Model
DER	Data Evaluation Report
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the time required to observe a 75% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
DU	dust or powder
dw	dry weight
DWLOC	drinking water level of comparison
EBDC	ethylenebis(dithiocarbamate)
EC_{05}	effective concentration on 5% of the population
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EChE	erythrocyte cholinesterase
EDE	estimated daily exposure
EEC	expected environmental concentration
EP	end-use Product
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
ETU	ethylene thiourea
EXAMS	Exposure Analysis Modeling System
F_0	parental generation
F_1	first filial generation
F_2	second filial generation

FC	food consumption
FIR	food ingestion rate
FOB	functional observational battery
g	gram(s)
GAP	good agricultural practice
GC-FPD	Gas Chromatography-Flame Photometric Detector
GC-MSD	Gas Chromatography-Mass Selective detector
GC-NPD	Gas Chromatography-Nitrogen Phosphorous Detector
ha	hectare(s)
Hct	hematocrit
HDT	highest dose tested
Hg	mercury
Hgb	hemoglobin
HPLC	high performance liquid chromatography
IPM	Integrated Pest Management
IRED	Interim Reregistration Eligibility Decision (USEPA Document)
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint WHO/FAO Meeting on Pesticide Residues
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol–water partition coefficient
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	lethal concentration to 50% (a concentration causing 50% mortality in the test population
LD_{50}	lethal dose to 50% (a dose causing 50% mortality in the test population)
LDT	lowest dose tested
LMA	locomotor activity
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)
m^3	metre(s) cubed
MA	motor activity
MBS	market basket survey
mg	milligram(s)
mL	millilitre(s)
mm	millimetre(s)
MMAD	mass median aerodynamic diameter
MoA	Mode of Action
MOE	margin of exposure
MRID	USEPA's Master Record Identifier number

MRL	Maximum residue limit
MS	mass spectrometry
MTD	maximum tolerated dose
N/A	not applicable
N/R	not required
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NRA	Australian National Registration Authority for Agricultural and Veterinary Chemicals
NTE	neuropathy target esterase
NTP	National Toxicology Program
OC	organic carbon content
OM	organic matter content
OP	organophosphate
OR	Odds Ratio
PChE	plasma cholinesterase
PDP	Pesticide Data Program (United States data)
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRZM	Pesticide Root Zone Model
PSI	pre-slaughter interval
Q_1^*	cancer potency factor
RBC	red blood cells
RED	Reregistration Eligibility Decision (USEPA Document)
REI	restricted entry interval
RfD	reference dose
RSD	relative standard deviation
S9	mammalian metabolic activation system
$t_{1/2}$	half-life
T3	triiodothyronine
T4	thyroxine
TC	transfer coefficient
TGAI	Technical Grade Active Ingredient
TOCP	tri-*ortho*-cresylphosphate
TPM	triophanate-methyl
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
USC	Use Site Category
UV	ultraviolet
µg	micrograms

µm	micrometer
µg	micrograms
v/v	volume per volume dilution
↓ -	decreased
↑ -	increased
♂ -	males
♀ -	females
1/n	exponent for the Freundlich isotherm

Appendix I Metiram Products Registered in Canada (Excluding Discontinued Products or Products with a Submission for Discontinuation) as of 31 October 2012

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (metiram)
20084	Technical	BASF Canada Inc.	Technical Metiram (Polyram)	Solid	89%
20087	Commercial	BASF Canada Inc.	Polyram DF Water Dispersible Granular Fungicide	Wettable granules	80%
30395	Commercial	BASF Canada Inc.	Cabrio Plus	Wettable grasnules	55%

Appendix II Commercial Class Uses of Metiram Registered in Canada, Excluding Uses of Discontinued Products or Products with a Submission for Discontinuation as of 31 October 2012

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (kg a.i./ha)		Maximum Number of Applications per Year[1]	Typical Number of Days Between Applications[1]	Registrant Supported Use?	Comments
				Maximum Single	Maximum Cumulative				
Use-site Category 10: Seed Treatments Food and Feed									
Potato seed treatment	Seed borne common scab, Fusarium seed piece decay	Dust or Powder	Not stated	1.45-2.10	2.90-4.20	1 or 2 (if treated whole seed is cut after initial treatment)	Not stated	No	Two treatments are rare.
Use-site Category 13: Terrestrial Feed Crops; Use-site Category 14: Terrestrial Food Crops									
Apple	Apple scab, cedar apple rust, apple quince rust	Wettable Granules	Ground,	3.6-4.8	14.4-19.2	Not stated [4]	Not stated [7]	Yes	
	Apple scab, powdery mildew			2.40 kg metiram/ ha + 0.136 kg myclobutanil/ha as a tank-mix	14.4 kg metiram / ha + 0.816 kg myclobutanil/ha as a tank-mix	Tank-mix application: 6	Not stated [7]	Yes	
Potato	Early blight, late blight		Ground and aerial	0.88-1.8	8.8-18.0	Not stated [10]	5	Yes	
Use-site Category 14: Terrestrial Food Crops									
Asparagus	Rust	Wettable Granules	Ground	1.8-2.6	7.2-10.4	4	7	Yes	
Carrot	Cercospora blight, alternaria blight			1.8	7.2	Not stated [4]	7	Yes	
Celery	Early blight, late blight			1.8-2.6 kg/ha	7.2-10.4	Not stated [4]	7	Yes	
Grape	Downy mildew, black rot	Wettable Granules		1.6 kg/1000 L water = 1.6 kg/ha	4.8	3	Not stated [7]	Yes	
		Dust or Powder		3.52-4.64	10.56-13.92			No	

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (kg a.i./ha)		Maximum Number of Applications per Year[1]	Typical Number of Days Between Applications[1]	Registrant Supported Use?	Comments
				Maximum Single	Maximum Cumulative				
Sugar beets	Cercospora leaf spot	Wettable Granules	Ground	1.8	3.6	Not stated [2]	7	Yes	
Tomato	Anthracnose, Septoria leaf spot			2.6	10.4	Not stated [4]	7	Yes	
	Early blight, late blight, gray leaf spot	Wettable Granules		1.8	7.2			Yes	

Footnote:

[1] Values in square brackets [ ] were proposed by the registrant.

Appendix III Uses of Metiram in Canada for Those Site-Pest Combinations of Commercial Class Products for which Risk Concerns Have Been Identified

Site(s)	Pest(s)	Supported Use of metiram?[1]	Concerns from Risk Assessments[2]?	Identification of Risk Assessment Concerns
Use-site Category 10: Seed Treatment				
Potato seed treatment	Seed borne common scab, Fusarium seed piece decay	No	Yes	N/A
Use-site Category 13: Terrestrial Feed Crops, Use-site Category 14: Terrestrial Food Crops				
Apple	Apple scab, cedar apple rust, apple quince rust, powdery mildew	Yes	Yes	See Sections 3.0 and 4.0.
Potato	Early blight, late blight	Yes	Yes	See Sections 3.0 and 4.0.
Use-site Category 14: Terrestrial Food Crops				
Asparagus	Rust	Yes	Yes	See Sections 3.0 and 4.0.
Carrot	Cercospora blight, alternaria blight	Yes	Yes	See Sections 3.0 and 4.0.
Celery	Early blight, late blight	Yes	Yes	See Sections 3.0 and 4.0.
Grape	Downy mildew, black rot	Yes	Yes	See Sections 3.0 and 4.0.
Sugar beets	Cercospora leaf spot	Yes	Yes	See Sections 3.0 and 4.0.
Tomato	Anthracnose, Septoria leaf spot, early blight, late blight, gray leaf spot	Yes	Yes	See Sections 3.0 and 4.0.

[1] Yes = use is supported by the registrant; Partial = the registrant does not support dust/powder formulation for use on this site; and

No = the registrant does not support this use.

[2] Yes = there are risk concerns for this use.

Appendix IV Toxicity Profile and Endpoints for the Health Risk Assessment for Metiram and ETU

Table 1 Toxicology Profile for Metiram from PMRA and foreign reviews

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption Distribution Metabolism Excretion Rat, strain unknown Up to 5/sex PMRA #1252882	a) 5/sex: 5 mg/kg for 14d, then labelled dose of 5 or 50 mg/kg bw b) 3/sex, single dose of 5 or 50 mg/kg bw, after bile duct cannulation, sacrificed 48h later c) 5/sex, 5 or 50 mg/kg bw, blood taken @216h d) 5/sex, 5 mg/kg bw/d for 7 days, 1/sex killed at 4, 24, 72, 120 and 168h e) same as d), only the rat was autoradiographed f) 1 ♂, single dose of 5 mg/kg bw, autoradiography at 24h g) 1 rat/sex with cannulated bile ducts, 10 mg/kg bw, bile collected at 0-12 and 12-24h h) 3/sex, single dose of 100 mg/kg bw, urine collected for 24h postdose i) 3 ♂, 0.5 mg/kg bw ETU.	**Absorption:** incompletely via GI (oral admin). Lower doses more easily absorbed. **Distribution:** Peak plasma concs at 4 and 6h (5 and 50 mg/kg bw, resp). After repeat dosing (5 mg/kg bw/day, 7 days), residues found in thyroid and the kidneys (♀ >♂). **Metabolism:** Metabolites in urine, bile and kidney: EDA, N-acetyl-EDA, ethanolamine, oxalic acid, EU, ETU (10-35%), and EBIS. Trace EU and ETU found in liver. **Excretion:** 98% excreted within 48h. 54 - 78.7% in feces 21.3 - 46.6% in urine 0.4 - 1.1% in expired air. Patterns of excretion were noted to be similar regardless of single or repeat exposure patterns. **Biliary excretion of radioactivity**: 5 mg/kg bw: (♂) 14.3; (♀) 7.1% 50 mg/kg bw: (♂) 4.3%; (♀) 3.7%	
Acute Toxicity Studies (not corrected for purity)			
Numerous oral mouse and rat studies n=10 (not specified for all studies) PMRA # 1228700, 1589544, 1589542, 1589544, 1821742, 1821759, 1821765, 1589541	Limit doses 5 - 12,000 mg/kg bw	LD_{50} > 5000 mg/kg bw **Low acute oral toxicity**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Dermal / Rat - SD (Sex, # not specified) PMRA # 1589551	Limit dose of 2000 mg/kg bw Purity: 77.5% active + 2% ETU	LD_{50} > 2000 mg/kg bw **Low acute dermal toxicity**	
Inhalation (4 h) / Rat - SD (Sex, # not specified) PMRA # 1589603	Limit dose of 5.7 mg/L Purity: 77.5% active + 2% ETU	LC_{50} > 5.7 mg/L **Low acute toxicity**	
Dermal Irritation / Rabbits (Sex, #, strain not specified) PMRA #1209689	50% aqueous paste of 80% dispersible powder	No irritation noted at 24 hours, however study is **supplemental** - no study details provided and the applied dose not recorded.	
Eye Irritation PMRA #1209690		**Non-irritating**	
Skin sensitization (max) / Guinea Pigs n=6, Sex, strain not specified PMRA # 1230459	0.2 ml Freund's adj; 0.2 ml test substance, challenged with 0.3 g (1 wk) and 15 g test substance (2 wk)	**First challenge:** controls: erythema (3/6). Treated: erythema (6/6). **Second challenge:** controls: slight erythema (2/6). Treated: slight to distinct erythema (8/11). After 72 hrs, 6/11 animals showed scaling. **Potential Sensitizer**	
Subchronic Toxicity Studies			
3 month dietary/ Mice - $B_6C_3F_1$ 10/sex/group PMRA # 1589539	♂: 0, 84, 302, 853, or 2367 mg/kg bw/day ♀: 0, 133, 465, 1448, or 3565 mg/kg bw/day Purity: 95%, ETU: 2%	84 ♂ /133 ♀	**≥ 302/465 mg/kg bw/d:** ↓ bwg, ↓ serum T_4 (♀) **≥ 853/1448 mg/kg bw/d:** Thyroid: minimal to slight hypertrophy and vacuolation of the follicular epithelium; ↑abs and rel adrenal gland wt, ↑severity of fatty degeneration of 'X zone' in adrenal glands (♀), ↑rel liver wt (♂) **2367/3565 mg/kg bw/d:** ↓ bw and bwg (♂), ↑ serum T_3 (♂), ↑ rel liver wt (♀), ↑ abs liver wt (♂)
13-week dietary and neurotox addendum/ Rat - Wistar 13 rats/sex/group Unpublished study as well as a published article on the unpublished study. PMRA #1570233	♂: 0, 0.4, 5.8, 23.5, or 73.9 mg/kg bw/d ♀: 0, 0.4, 6.7, 27.3, or 88.8 mg/kg bw/d Purity: 95% ETU: 2%	6.7 Used for short-term dermal exposure	**≥6.7 mg/kg bw/d**: ↓ forelimb grip strength (90-days, ♀) **≥23.5/27.3 mg/kg bw/d**: ↓ RBC, ↓ Hb (♀), ↓ Ht (♀), ↓ P (♂), ↑ serum T_3 (♂) **73.9/88.8 mg/kg bw/d**: ataxia, ↓ bw, bwg creatinine, Ca^{2+}, and Mg^2; ↑ rel thyroid wt, ↓ T_4; ♀: ↓ forelimb and hindlimb grip strength, without neuropath or morphological changes in CNS or PNS, ↓ T_4, ALAT, ALP, K^+, and Na^+, ataxia and ↓ mylination of sciatic, sural and tibial nerves (3 ♀); ♂: ↓ urea, ↓ liver, kidney and testis wt, ↑ rel and abs thyroid wt

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
13 week dietary / Rat - SD 35 rats/sex/group PMRA # 1589582	♂: 0, 3, 6, 20, or 61 mg/kg bw/day ♀: 0, 4, 8, 24, 76 mg/kg bw/day Purity: 96.8% ETU: 2.2%	6/8	**≥ 3/4 mg/kg bw/d**: ↓ thyroid uptake of ^{131}I (♂) **≥ 6/8 mg/kg bw/d:** ↓ thyroid uptake of ^{131}I (♀) **≥ 20/24 mg/kg bw/d:** ↓ T$_4$, ↑ atrophy of muscle fibres (associated with proliferation of sarcolemmal nuclei), ↑ abs thyroid wt (♀) **61/76 mg/kg bw/d:** ↓ bw, ↓ fc, ↑ hind limb paralysis, slight to minimal thyroid hyperplasia (♂)
13 week inhalation / Rat - SD 28 rats/sex/group PMRA # 1589562, 1589561	0, 2, 20, or 100 mg/m^3 of **metiram** Purity: 94% ETU concentrations at 0, 0.02, 0.33, or 1.8 mg/m^3	2 mg/m^3 (0.54 mg/kg bw/d) Used for short and intermediate inhalation exposure	**≥ 20 mg/m^3:** "subacute alveolitis", characterized by accumulations of alveolar macrophages within alveolar lumen, accompanied by some polymorphonuclear leukocytes (thought to be a non-specific dust reaction); ↓ bwg (11-14%) **100 mg/m^3:** 1/sex: intra-alveolar pigment deposition,↑ mean lung/trachea wts.,↓ terminal bw (♂) No effect on thyroid.
21 day dermal / Rabbit - NZW 5 rabbits/sex/group PMRA # 1212846	0, 25, 50, or 250 mg/kg/day of **Polyram DF** (80% metiram), not corrected for ai	Irritation 50 Systemic > 250	**Irritation** **250 mg/kg bw/d:** minimal to moderate exfoliation and ulcerative dermatitis Thyroid and thyroid hormones not examined.
4 week dietary / Dog - Beagle 4 dogs/sex/group PMRA # 1570258	♂: 0, 5, 14, 28, or 41 mg/kg bw/d ♀: 0, 5, 15, 27 or 43 mg/kg bw/d Purity: 96.8% ETU: 2.2%	27	**≥ 27/28 mg/kg bw/d:** ↑ liver wt **41/43 mg/kg bw/d:** ↓ RBC, Hb, packed cell volume; ↑ frequency of micro-follicles in the thyroids (associated with minimal depletion of colloid and minimal hyperplasia of the follicular epithelium in 2/4 ♂ and 2/4 ♀)
52 week dietary / Dog - Beagle 5 dogs/sex/group PMRA # 1589583	♂: 0, 0.9, 2.5, 29.8, or 76.9 mg/kg bw/d ♀: 0, 1.1, 2.7, 29.9, or 92.7 mg/kg bw/d Purity: 93.6% ETU: ≤ 0.2%	2.5 Used for ADI and intermediate dermal exposure	**≥ 29.8/29.9 mg/kg bw/d**: ↓ fc (♀), ↑ follicular hyperplasia and thickening of the thyroid, ↓ serum T$_4$ (♂), slight anemia, ↑ incidence of focal hepatic lipofuscin pigment deposition;↑ lipid, cholesterol, triglycerides, phospholipids, ALP, and total protein; ↓ albumin and A/G ratio **76.9/92.7 mg/kg bw/d:** ↓ bwg and fc (especially in ♂), ↓ serum T$_4$ (♀), ↑ thyroid size and wt, ↑ reticulocytes

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
26 week oral (gavage) / Monkey - Rhesus 4 monkeys/sex/dose PMRA # 1228706	0, 5, 15, or 75 mg/kg bw/d Purity: 96.8% ETU: 2.2%	5	**≥ 5 mg/kg bw/d:** decline in T_4 (reversible) with no histopathological changes, ↓ iodine levels in thyroid (wks 1 and 8; considered to be adverse) **≥ 15 mg/kg bw/d:** ↓ T_3 and T_4, ↓ plasma iodine levels, ↑ protein-bound plasma iodine↑ thyroid wt, enlarged thyroid, minimal thyroid follicular hyperplasia (2/6), cuboidal cells in some thyroid follicles **75 mg/kg bw/d:** ↑ salivation occurring at time of dosing, ↑ liver wt (not associated with histopathological findings), minimal thyroid follicular hyperplasia (6/6)
26 week oral thyroid function (gavage) / Monkey - Rhesus 2 monkeys/sex/dose PMRA # 1228706	0, 5, or 75 mg/kg bw/d Purity: 96.8% ETU: 2.2%	5	Salivation occurred at the time of dosing, intermittently, in most treated animals. **≥ 5 mg/kg bw/d:** initial ↓ in iodine uptake followed by significant ↑ in uptake during latter part of the study (no correlation to thyroid hormone levels or morphological alterations); 1 animal vomited immediately after dosing **75 mg/kg bw/d:** 1♂ died (bronchopneumonia) and 2 animals vomited immediately after dosing; bilateral conjunctivitis (1 ♂), capsular damage on eye lense (gone by 23 weeks, 1 ♀), ↓ total plasma iodine, ↑ plasma-bound iodine (wks 16 and 27), enlarged thyroid (♀); ↑ thyroid wt, ↓ thyroid activity (wks 1, 4, and 8, unchanged at wk 16, and ↑ wk 27), similar trend for protein bound iodine, ↑ radioactivity but no change in protein bound activity in thyroids 48 hrs after last injection; ↑ liver wt
Chronic Toxicity/Oncogenicity Studies			
88+ week dietary / Mice - CFLP 52 mice/sex/group PMRA # 1230445, 1228711	♂: 0, 8, 24, or 79 mg/kg bw/day ♀: 0, 9, 29, or 95 mg/kg bw/day Purity: 96.8% ETU: 2.2%		88 weeks for ♀ and 96 weeks for ♂. **≥ 24/29 mg/kg bw/d:** ↓ bwg (first 14 wks, ♀) **79/95 mg/kg bw/d:** ↓ fc (♂), ↑ benign liver cell tumour incidence (21% vs 6% in controls, ♂) (ETU has liver tumours in ♀) **Study considered supplemental**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
111+ week dietary / Rat-/ SD 80 rats/sex/group (30 rat/sex/group for satellite) PMRA # 1230454, 1230456	♂: 0, 0.2, 0.8, 3.1, or 12.3 mg/kg bw/day ♀: 0, 0.2, 1.0, 3.8, or 15.5 mg/kg bw/day Purity: 96.8% ETU: 2.2% ETU 5.3 µCi ^{131}I i.v. from the plasma and incorporation into thyroid to assess thyroid function (3 rats/sex/dose level). Satellite groups used for blood and thyroid tests, organ weight analysis, and gross necropsy, were killed at 102 weeks.		111 wk study for ♂; 119 wk study for ♀. During week 3, rats in all groups showed signs of sialidacryoadenitis, a viral disease occasionally seen in rats of this strain. This may have affected the integrity of the study. Mortality rates were high, all doses (including control). **12.3/15.5 mg/kg bw/d:** ↑ incidence and severity of muscular atrophy, ↓ T_4 (wks 5, 7 and 51, ♀), ↑ T_3 (wks 103, 119, ♂; wk 77, ♀), ↑ pituitary adenomas(74% vs 58% in controls, ♀) **Study considered supplemental**
ETU 2 yr Mouse feeding study, with repro dosing / Mice - B6C3F1 variable #/sex/dose n = 60 10/sex/dose sacrificed at 9 months PMRA # 1570233	**Perinatal**: 0, 33, 110 and 330 ppm **Adult**: 0, 330, 1000 ppm for 2 yrs, one group received 100 ppm for 2 yrs Standard adult conversions 100, 330 and 1000 ppm = 15, 49.5 and 150 mg/kg bw/d. Purity: 99% Study combined a perinatal exp (in utero and throughout suckling) with traditional NTP chronic bioassay. Female mice (F) generation) were fed a diet of 0, 33, 110 or 330 ppm ETU for 1 wk before breeding. After mating all females were kept on the ETU diet. On postpartum day 7 the litters (F1) were standardized to 8, weaned on day 28 and separated by sex. Exposure continued and at 8 weeks the pups were divided into 60/sex at concentrations of 0, 330 and 1000 ppm.	**F0:F1 ppm treatments were as follows:** 0:0, 0:330, 0:1000, 330:0, 330:330, 330:1000, 33:100, 110:330 9 months All adult exposed mice had centrilobular hepatocellular cytomegaly, ↑ hepatocellular adenomas. **1000 ppm** ♀: eosinophilic foci. ↑ abs and rel liver wts in groups receiving adult concentrations, regardless of perinatal exp.↑ abs thyroid wts, T_3 and TSH (♂). 2-years Except for perinatal-only exp, all doses had ↓ bw. **Perinatal-only Exp**: no effects noted. **Adult-only Exp (330 and 1000 ppm)**: Thyroid: diffuse cytoplasmic vacuolization, focal hyperplasia, and neoplasia. **1000 ppm**: follicular cell adenomas or carcinomas with multiple or bilateral neoplasms (70%). ♀ more susceptible. Liver: diffuse centrilobular hepatocellular cytomegaly, marked ↑ in hepatocellular adenomas/carcinomas (♀). **1000 ppm**: ↑ hepatocellular carcinomas (♂). Multiple hepatocelluar neoplasms, with carcinomas metastasizing to the lung. Rare hepatoblastomas also occurred, particularly in ♂. Pituitary: **1000 ppm**: ↑ focal hyperplasia or adenoma of pars distalis (♂) and ♀: ↑ adenoma (but not hyperplasia). **Combined Perinatal-Adult Exp:** Thyroid, Liver, Pituitary: **330-330 ppm**: marginal ↑ of non-neoplastic and neoplastic lesions in all 3 organs compared to adult exposure, but this marginal ↑ not seen at the 330-1000 ppm dose. ♂: all had a marginal↑ in follicular cell hyperplasia compared to	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
	10/sex were sacrificed at 9 months and 50/sex were sacrificed after 2 years.	adult-only exposure.	
2 yr feeding study, with repro dosing / Rats - Fischer F44 variable #/sex/dose, n = 60 10/sex/dose sacrificed at 9 months This study is part of the onco mouse study reported above. PMRA # 1570233	**Perinatal**: 0, 9, 30, 90 ppm **Adult**: 0, 25, 83 and 250 ppm for 2 yrs. Standard conversions would be 1.25, 4.15 and 12.5 mg/kg bw/d Purity: 99% Female rats were fed a diet containing 0, 9, 30 or 90 ppm ETU for 1 wk before breeding. After breeding, dosing continued and on PND 4 litters were standardized to 8 and weaned on day 28. Pup exposure continued for 8 wks and then divided into grps of 50/sex and exposed to adult concentrations of 0, 25, 83, and 250 ppm. *This study, combined with the Schmid study above, fulfills the chronic/onco rat data requirement.	**F0:F1 ppm treatments were as follows:** 0:0, 0:83, 0:250, 90:0, 90:83, 9:250, 30:83 and 9:25 ppm 9 months **0-83, 0-250, 90-83 and 90-250 ppm**: ↑ abs and rel liver wt (♂), **0-250 and 90-250 ppm:** ↑ thyroid wt. **0-83, 0-250, 30-83, 90-83 and 90-250 ppm**: ↑ thyroid follicular cell hyperplasia **90-250 ppm:** ↑ thyroid follicular cell adenomas. Except for **90-0 ppm**, all dose groups had ↓ T_4 and ↑ TSH. 2-yr **Perinatal-only Exp:** Thyroid: ↑follicular cell hyperplasia (dosed animals 18-64%, conrol: 0-9%) **Adult-only Exp:** Thyroid: **0:83 ppm:**↑ follicular cell hyperplasia **(58% vs 2% in control ♂, ♀: 16% vs 4% in control)** , adenomas **0-250 ppm**: follicular cell carcinomas, ♂ appear more sensitive. Some carcinomas invaded the adjacent parenchyma and/or esophagus and trachea, and two metastasized to the lungs. Thyroid tumour incidence in adult-only exposure was (1/49, 12/46, 37/50 for males and 3/50, 7/44, 30/49 at 0, 83 and 250 ppm, resp) **Combined Perinatal-Adult Exp:** Thyroid: **90-83 and 90-250 ppm**: ↑ follicular cell hyperplasia (♂), this was greater than that observed at 0-83 ppm, indicating some type of perinatal action. There was a similar effect with follicular adenomas/carcinomas. For males, tumour incidence was as follows: 3/46, 14/47, 13/50 and 48/50 for 9:25, 30:83, 90:83 and 90:250 ppm exposures, resp. Other Organs: **90-83 and 90-250 ppm**: ↑ neoplasms of the Zymbal's gland and mononuclear cell leukaemia.	
ETU, a metabolite of the ethylenebis(dithiocarbamate) (EBDC) fungicides, is currently classified by the USEPA as a B2 carcinogen, with a q_1*= 0.0601 (mg/kg/day)$^{-1}$. The low dose extrapolation for human risk assessment is based on liver tumours in female mice. The PMRA concurs with this assessment and considers ETU to be the metabolite of concern for cancer with all EBDC fungicides.			
Reproductive and Developmental Toxicity Studies			
Three generation Reproduction/ Teratology study (dietary) / Rats - SD 12 ♂, 24 ♀/dose PMRA # 1230447	0, 5, 40, 320 ppm (♂: 0, 0.2, 1.8, or 14.2 mg/kg bw/d ♀: 0, 0.3, 2.2, or 19.8 mg/kg bw/d) 2nd mating of F_2 served as the teratology study (GD		**F0:** 1st mate: mid and high dose was ↓ 8-17%, 2nd mate: mid ↓ 13%, high only 4.3% **F1:** 1st mate: low and mid ↓ 14%, high ↑ 10% 2nd mate: low ↓ 35%, mid ↓ 14%, high ↑ 10% **F2:** 1st mate: low ↓ 17%, mid 14%, high 26% 2nd mate: low ↓ 13%, high 18%

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
	20 examination) Purity: 96.8% ETU: 2% No histopathology of reproductive organs or target organs, results highly variable, F3 pups infested with nematodes		As well, there was inconsistent ↑s in precoital time in the high dose **Offspring:** Although there appears to be no effect on the offspring, lack of detailed reporting and highly variable survival, bw and bwg among the pups, litters and generations preclude a meaningful assessment. **EPA maternal bw**: sets provisional NOAEL at 2.2 based on bw changes during gestation/lactation. PMRA notes that bw was also highly variable. **F0**: 1st mate: ↓ 5-6% (gestation) 2nd mate: ↓ 8% gestation, 5-8% postpartum **F1**: 1st mate: ↓ 9-10% gestation, 7-12% postpartum 2nd mate: 7-10% gestation, 3-5% postpartum **F2**: no real weight changes (1-2%) for 1st and 2nd mating. Pregnancy rates were highly variable throughout the study. **Study considered supplemental**
Teratology oral (gavage) / Rats - SD 20 ♀ rats/dose gd 6-15 PMRA # 1230462	0, 40, 80, or 160 mg/kg bw/d Purity: 96.8% ETU: 2.2%	Maternal LOAEL 40 Developmental 80 Used for ARfD	Maternal effects: **≥40 mg/kg bw/d:** ↓ bw and bwg (corrected, day 20) Fetal effects: **160 mg/kg bw/d**: ↓ live litter size and litter wt, ↑ postimplantation loss
Teratology oral (gavage) / Rabbits - Himalayan 15 ♀/dose gd 7-19 PMRA # 1589585, 1589586	0, 10, 40, or 120 mg/kg bw/day Purity: 97.9% ETU ≤ 0.2% Did not do detailed examine of the heads, however no gross malformations.	Maternal 10 Developmental 10	Maternal Effects: **≥40 mg/kg bw/d:** ↓ bw, fc, defecation; ↑ abortions **120 mg/kg bw/d:** 1 death Fetal Effects: **40 mg/kg bw/d:** abortions (2/15) **120 mg/kg bw/d:** abortion (8/15); ↓ fetal bw, ↑ irregular shaped sternebrae and total skeletal variations **Study considered supplemental.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Genotoxicity Studies			
in vitro			
reverse mutation assay TA 98, 100, 1535, 1537 PMRA # 1230451	0, 1, 10, 50, 100, 500, 2500 µg/plate TGAI + 2.2% ETU		**Negative** (+S9) (derived from rat or mouse) **Negative** (-S9)
point mutation HGPRT locus of CHO cell line, K1 PMRA # 1589596	0.5, 1, 5, 10, 50, 100, 500 µg/ml TGAI **Premix:** 95%		**Negative** (± S9)
SCE CHO, WB1 PMRA#1589552	0, 40, 60, 80, 100, 125, 150, 175, 200 µg/ml TGAI + 2.2% ETU		**Positive** (± S9, mouse derived) **Negative** (-S9, rat derived)
SCE CHO PMRA#1589552	0, 40, 60, 80, 100, 125, 150, 175, 200 µg/ml TGAI+ 2.2% ETU and 42.7 cleavable CS_2		**Positive** (± S9, mouse derived) **Negative** (± S9, rat derived)
Rec assay and Reverse mutations B. Subtilis strains H17 (rec+) and M45 (rec-) and TA1535-TA1538 and E. Coli strain WP2 PMRA#123045			**Negative**
Transformation promotion / Mice - embryo fibroblasts C3H-10T ½ (clone 8) PMRA # 1589536	0, 0.1, 0.25, 0.5, 0.75, 1.0 µg/ml ETU: 2.2%		Transformation: **negative** Promotion activity: **weakly positive**
Unscheduled DNA synthesis / Rats - (hepatocytes ♂) PMRA # 1589538	0.492, 1.23, 2.46, 4.92, 12.3, 24.6, 49.2, 160 µg/ml metiram + 2.2% ETU		**Negative**
Alkaline Elution Studies in cells of multiple organs / Rats PMRA # 1831830	120 and 1200 mg/kg of **Polyram** (80% metiram)		**≥ 120 mg/kg**: single stranded DNA breaks were noted in liver and kidney cells

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
in vivo			
SCE CHO, LMP stock (bone marrow) PMRA # 1589552	1000, 3330, 10000 mg/kg bw **Premix:** 95%	**Negative**	
Chromosome aberration Rats - Fisher 344 (♂ bone marrow) PMRA#1589536	0, 0.24, 1.2, 2.4 g/kg bw (single dose) 0, 0.02, 0.1, 0.2 g/kg bw (5 repeated oral doses) ETU: 2.2%	**Negative**	
Dominant lethal / Mice - CD1 (♂) 20 mice/dose PMRA#1230450	0, 300, 600, 1200, 2400 mg/kg bw/d ETU: 2.2%	**Negative**	

Table 2 Toxicology Profile for ETU

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption Distribution Metabolism Excretion Published and unpublished data for mouse, rat, guinea pig, cat and monkey PMRA # 1805552, 1805550, 1805647, 1619137, 1805547	Various dose levels and routes	Absorption: rapid from the digestive tract. Uptake through intact skin is relatively slow. Regardless of absorption pathway, ETU accumulates primarily in the thyroid. Distribution/accumulation in the rat was as follows: thyroid>kidney>liver>brain>heart>spleen>muscle>lung>fat. ETU half-life was 28h in monkey, 9-10 hours in rat and 5 hours in the mouse. Excretion: complete and primarily in the urine (50-80%, depending on species) at 48h. Metabolism: more rapid in the mouse, compared to the rat. However, metabolism is more extensive in the rat. Metabolites include EU and other polar metabolites.	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Absorption Distribution Metabolism Excretion Published and unpublished studies in mouse, rat, guinea pig PMRA # 1619136, 1805608, 1805575, 1570232	Various dose levels and routes	During all of gestation, ETU in amniotic fluid, placenta and fetal carcass correlated with maternal blood levels, but levels ↑ in maternal livers. During postpartum, ETU in maternal liver and milk was 10 and 2x > than maternal blood. Levels in maternal milk were 13x neonatal levels. Pre-treatment did not alter ETU kinetics in postpartum dams / neonates. Radioactivity peaked in mice and rats at 1.3 and 1.4 hours, respectively; maternal and fetal tissues were similar at 3 h posttreatment. The t½ for ETU elimination from maternal blood was 5.5 and 9.4 hours in mice and rats, respectively. Main route of excretion was the urine with 74 and 70% in the mouse and rat, respectively. 40% metabolites in the mouse, compared to 95% in the rat. The mouse appears to have a more rapid metabolism of ETU, while the rat is more extensive. This could be the reason developmental toxicity more severe in rat than mouse. Radioactivity in the fetus peaked at 2 h. ETU distributed homogenously throughout tissues, except thyroid (↑ in activity for first 24h). No sig difference in T4 between treated and control maternal serum, but stat sig ↑ in malformed fetuses (100%) at 100 mg/kg bw.	
Acute Toxicity Studies			
Oral Mice, non-pregnant and pregnant (gd 9) PMRA # 1805563, 1805631, 1570258		LD50 2400-4000 mg/kg bw (>3000 mg/kg bw for pregnant mice) **Low Toxicity**	
Oral Rats, non-pregnant and pregnant (gd 13) PMRA # 1570258, 1805631, 1805563, 1805536		LD50: 545-1832 mg/kg bw (600 mg/kg bw for pregnant rats) **Moderate Toxicity**	
Oral Hamsters, non-pregnant and pregnant (gd 11) PMRA # 1570258, 1805631		LD50>2400 mg/kg bw **Low Toxicity**	
Dermal rabbit PMRA# 1521628		LD50>2000 mg/kg bw **Low Toxicity**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Inhalation Rats, SD PMRA# 1521628		LC50 >10.4 mg/L	
Dermal irritation Rabbits, NZW PMRA# 1570258		**Not a dermal irritant**	
Eye irritation Rabbits, NZW PMRA# 1570258		No irritation noted, however UV light was not used with flouroscein staining.	
Sensitization Guinea Pigs,Hartley PMRA # 1805564	10 female Maximization	**Potential Sensitizer**	
Sensitization Mice, B6C3F1 ♀ PMRA # 1570258	Maximization	**Not a Sensitizer**	
Subchronic Toxicity Studies			
90-day, dietary Mice, CD-1 15/sex/dose PMRA # 1570233	0, 0.16, 1.7, 18, 168 mg/kg bw/d (♂) 0, 0.22, 2.4, 24, 230 mg/kg bw/d (♀)	1.7 Used for short-term aggregate exposure, general population	**≥18 mg/kg bw/d**: ↑ rel liver wt (♀), ↑ thyroid follicular cell hyperplasia, ↓ colloid density. **168 mg/kg bw/d**: ↑ mixed function oxidase activity, abs and rel thyroid wts, follicular epithelial cytoplasmic vacuolation and interstitial congestion, ↑ centrilobular hypertrophy, nuclear pleomorphism and intranuclear inclusions in the liver. ♂: ↑ abs and rel liver wts
90-day, dietary Rats, SD 60/sex/dose PMRA # 1831764	1, 5, 25, 125, 625 ppm (0.07, 0.35, 1.7, 6.25, 31.25 mg/kg bw/d) Purity: 96.8%	1.7	Liver congestion evident with dose and time. **≥6.25 mg/kg bw/d**: hyperaemia of the thyroid, with and without enlargement, ↑ rel (to brain) thyroid wt and ↓ ^{125}I uptake, thyroid binding globulin (TBG), T_3 and T_4. **31.25 mg/kg bw/d**: ↑ mortality, ↓ bwg, excessive salivation, hair loss, rough and bristly hair coat, scaly skin.
90-day, dietary Rats, SD 14/sex/dose Special, in combo with mancozeb PMRA # 1570229	**ETU**: 1 dose - 250 ppm (♂: 14.28 mg/kg bw/d ♀: 17.81 mg/kg bw/d) Purity: 99%	LOAEL: 14.28	**ETU**: **14.28/17.81 mg/kg bw/d**: ↓ bwg, fc; ↑ serum cholesterol, and rel liver and thyroid wt, ↓ T_4, ↑ T_3 and TSH, and thyroid lesions; centrilobular hepatocyte hypertrophy, ↓ hepatic MFO activity

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Sub-chronic, dietary Rats, Osborne-Mendel 20 ♂/dose Treated for 30, 60, 90 or 120 days PMRA # 1805536	0, 50, 100, 500 or 750 ppm (0, 2.5, 5.0, 25 and 37.5 mg/kg bw/d	2.5	**≥2.5 mg/kg bw/d**: ↑ rel thyroid wts (≥60 days) **≥5 mg/kg bw/d**: ↑ rel thyroid wt (≥30 days), ↓ ^{131}I uptake at 24 h, slight hyperplasia of the thyroid gland. **≥25 mg/kg bw/d**: ↓ bw, ^{131}I uptake (4 h) and stat sign after 90 days (up to 13x lower than control), moderate-marked hyperplasia of thyroid, lack of colloid and heightened epithelial walls, ↑ vascularization, follicular adenomas
13-wk, dietary Dogs 4/sex/dose PMRA # 1570230	0, 10, 150, 2000 ppm (♂: 0, 0.39, 6.02, 66.23 mg/kg bw/d ♀: 0, 0.42, 6.51, 71.62 mg/kg bw/d) Purity: 98%	0.39	**≥0.39/0.42 mg/kg bw/d**: ↓ AST (♀, wk 13) **≥6.02/6.51 mg/kg bw/d**: ↓ hgb, packed cell volume and RBCs, ↑ reticulocytes (♀), ↑ cholesterol and ↓ AST (♂) **66.23/71.62 mg/kg bw/d**: ♂: ↑ mortality (with ↓ bw), 2 that died had slight/ minimum focal seminiferous atrophy of the testis, glandular hypotrophy of prostate,↑ serum protein and globulin, and ↓ ALP, RBC, hemoglobin. ♀: ↓ activity, bilobed swelling in pharyngeal area, ↑ cholesterol. Both sexes had ↓ phosphorous, T_3, T_4 and ↑ thyroid, liver and adrenal wts, exophthalmia. Histo showed ↑ hypertrophy of basophilic cells of the pituitary (with micro-vascuolization), moderate involution of thymus, and severe follicular hyperplasia of thyroid (with papillary projections of follicular epithelium in the luman of the follicles).
1-yr, dietary Dogs 4/sex/dose PMRA # 1619162	0, 5, 50 and 500 ppm (♂: 0, 0.18, 1.99, 20.13 mg/kg bw/d ♀: 0, 0.19, 1.79, 20.15 mg/kg bw/d) Purity: 98%	0.18/0.19 Used for ADI and long-term dermal and inhalation exposure	**≥1.99/1.79 mg/kg bw/d**: 8% ↓ bw (♂ at 1 yr), ↓ terminal bwg (43% of control, ♂), ↑ thyroid wts. Hypertrophy of thyroid and colloid retention, pigment accumulation in liver (Kupffer's cells). **20.13/20.15 mg/kg bw/d**: ↑ mortality, pale mucous membranes, subdued behaviour, yellow/orange feces, ↓ terminal bw (15%), bwg (-60%), hgb, RBC (2 ♂ and 1 ♀ had anemia with 90% ↓ in hgb), packed cell vol, mean corpuscular hgb, platelet count, albumin/globulin ratio, T_3 and T_4 values (shortly before death). ↑ reticulocytes, mean corpuscular volume, total bilirubin, AST, ALT (♂ only), centrolobular hepatocellular necrosis of the liver (multifocal and moderately severe in ♂), hypertrophy of follicular cells with dilation of follicles in the thyroid, dyspnea and tachycardia.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Chronic Toxicity/Oncogenicity Studies			
2 yr Rats, SD 68/sex/dose NB: only tested for thyroid toxicity PMRA # 1805537, 1805539	0, 5, 25, 125, 250 or 500 ppm (0, 0.25, 1.25, 6.25, 12.5, 25 mg/kg bw/d) animals sacrificed at 2, 6, and 12 months 250 and 500 ppm animals sacrificed at 2 yrs	0.25	**≥0.25 mg/kg bw/d**: ↑ thyroid hyperplasia, no effects on thyroid hormones, or wt, unlikely adverse at this dose level. **≥1.25 mg/kg bw/d**: ↓ initial bw, ↑ vacuolarity of thyroid. **≥6.25 mg/kg bw/d**: ♂ ↑ thyroid wts; ♀ ↓ bw, ↑ rel thyroid wt, thyroids were hypofunctioning at 6 months but hyperfunctioning at 12 months. Development of nodular hyperplasia of thyroid after 1 yr. **≥12.5 mg/kg bw/d**: ↑ rel thyroid wt (♂) and ↑ thyroid wt (♀). ↑ thyroid carcinomas in 2 yr animals. **25 mg/kg bw/d**: ↓ survival, and ↑ pneumonia (complicated by obstruction of trachea by enlarged thyroid). ♂ had ↓ bw and ^{131}I uptake; ♀: hypo-functioning thyroid at 24 months Hypo vs hypernd thenfunctioning thyroid: ETU may initially ↓ thyroid activity, compensation occurs by ↑ release of TSH which stimulates thyroid wt., to overcome blocking effect of ETU. Progression to neoplasia may be a result of excessive pharm stimulation. This is supported, in part, by a lack of thyroid tumours at 1 yr at 5 or 25 ppm, and an ↑ in tumour incidence after 1 yr at 125 ppm, confirmed after 2 yrs (@ 250 and 500 ppm). **Study considered supplemental**
2-yr Rats, SD 30/sex/dose Interim sacrifice at 52 wks. NB: only looked at thyroid toxicity PMRA # 1570235	0, 0.5, 2.5, 5 or 125 ppm Purity: 96% EPA: analytical results of ETU in the feed varied widely, with large coefficients, and actual compound intake on a mg/kg bw could not be calculated.	0.5 ppm	Interim sacrifice: **≥2.5 ppm**: diffuse thyroid hyperplasia in ♂ at 52 wks. **≥5 ppm**: thyroid follicular cell hyperplasia. **125 ppm**: ↑ thyroid wt, diffuse or nodular enlargement of thyroid, T_3 and TSH, ↓ T_4. ♂: ↑ protein, albumin, GGT, cholesterol, bilirubin, and ↓ urea. ♀: ↓ glucose, ↑ uric acid. Histo. ↑ thyroid follicular hyperplasia, ↑ adenomas (♂) Minimal -slight focal/multifocal cellular hypertrophy of anterior pituitary (♂). Terminal sacrifice: **≥2.5 ppm**: excessive diffuse follicular hyperplasia of thyroid, slight-severe nodular hyperplasia, ↑ incidence of benign and malignant follicular neoplasms and anterior pituitary adenomas (♂). **Study considered supplemental**

<table>
<tr><th>Study/Species/ # of animals per group</th><th>Dose Levels/Purity of Test Material</th><th>NOAEL (mg/kg bw/day)</th><th>Results/Effects</th></tr>
<tr><td>2 yr with repro dosing (explained in results), dietary
Mice, B6C3F1

variable #/sex/dose
n = 60
10/sex/dose sacrificed at 9 months

PMRA # 1570233, 1805515</td><td>Perinatal: 0, 33, 110 and 330 ppm

Adult: 0, 330, 1000 ppm for 2 yrs,
one group received 100 ppm for 2 yrs
Standard adult conversions 100, 330 and 1000 ppm = 15, 50 and 150 mg/kg bw/d.
Purity: 99%

Study combined perinatal exp (in utero and throughout suckling) with traditional NTP chronic bioassay. Female mice (F) generation) were fed a diet of 0, 33, 110 or 330 ppm ETU for 1 wk before breeding. After mating all females were kept on the ETU diet. On postpartum day 7 the litters (F1) were standardized to 8, weaned on day 28 and separated by sex. Exposure continued and at 8 weeks the pups were divided into 60/sex at concentrations of 0, 330 and 1000 ppm. 10/sex were sacrificed at 9 months and 50/sex were sacrificed after 2 years.</td><td colspan="2">F0:F1 ppm treatments were as follows:
0:0, 0:330, 0:1000, 330:0, 330:330, 330:1000, 33:100, 110:330

<u>9 months</u>
All adult exposed mice had centrilobular hepatocellular cytomegaly, ↑ hepatocellular adenomas.
1000 ppm ♀: eosinophilic foci.
↑ abs and rel liver wts in groups receiving adult concentrations, regardless of perinatal exp. ↑ abs thyroid wts, T_3 and TSH (♂).

<u>2-years</u>
Except for perinatal-only exp, all doses had ↓ bw.

Perinatal-only Exp: no effects noted.

Adult-only Exp (330 and 1000 ppm):
<u>Thyroid:</u> diffuse cytoplasmic vacuolization, focal hyperplasia, and neoplasia.
1000 ppm: follicular cell adenomas or carcinomas with multiple or bilateral neoplasms (70%). ♀ more susceptible.
<u>Liver</u>: diffuse centrilobular hepatocellular cytomegaly, marked ↑ in hepatocellular adenomas/carcinomas (♀).
1000 ppm: ↑ hepatocellular carcinomas (♂). Multiple hepatocelluar neoplasms, with carcinomas metastasizing to the lung. Rare hepatoblastomas also occurred, particularly in ♂.
<u>Pituitary</u>: @1000 ppm: ↑ focal hyperplasia or adenoma of pars distalis (♂) and ♀: ↑ adenoma (but not hyperplasia).

Combined Perinatal-Adult Exp:
<u>Thyroid, Liver, Pituitary:</u> 330-330 ppm: marginal ↑ of non-neoplastic and neoplastic lesions in all 3 organs compared to adult exposure, but this marginal ↑ not seen at the 330-1000 ppm dose. ♂: all had a marginal ↑ in follicular cell hyperplasia compared to adult-only exposure.

See Appendix V1A for tumour tables.</td></tr>
<tr><td colspan="4">ETU is currently classified by the USEPA as a B2 carcinogen, with a $Q_1^* = 0.0601\ (\text{mg/kg/day})^{-1}$. The low dose extrapolation for human risk assessment is based on liver tumours in female mice. The PMRA concurs with this assessment and considers ETU to be the residue of concern for the cancer assessment of all EBDC fungicides.</td></tr>
</table>

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
2 yr with repro dosing, dietary Rats, Fischer variable #/sex/dose n = 60 10/sex/dose sacrificed at 9 months This study is part of the onco mouse study reported above. PMRA # 1570233, 1805515	**Perinatal**: 0, 9, 30, 90 ppm **Adult**: 0, 25, 83 and 250 ppm for 2 yrs. Standard conversions would be 1.25, 4.15 and 12.5 mg/kg bw/d Purity: 99% Female rats were fed a diet containing 0, 9, 30 or 90 ppm ETU for 1 wk before breeding. After breeding, dosing continued and on PND 4 litters were standardized to 8 and weaned on day 28. Pup exposure continued for 8 wks and then divided into grps of 50/sex and exposed to adult concentrations of 0, 25, 83, and 250 ppm. ***This study, combined with study above (PMRA # 1570235), fulfills the chronic/onco rat data requirement.**	**F0:F1 ppm treatments were as follows:** 0:0, 0:83, 0:250, 90:0, 90:83, 9:250, 30:83 and 9:25 ppm 9 months **0-83, 0-250, 90-83 and 90-250 ppm**: ↑ abs and rel liver wt (♂), **0-250 and 90-250 ppm:** ↑ thyroid wt. **0-83, 0-250, 30-83, 90-83 and 90-250 ppm**: ↑ thyroid follicular cell hyperplasia **90-250 ppm:** ↑ thyroid follicular cell adenomas. Except for **90-0 ppm**, all dose groups had ↓ T_4 and ↑ TSH. 2-yr **Perinatal-only Exp:** Thyroid: ↑follicular cell hyperplasia (dosed animals 18-64%, conrol: 0-9%) **Adult-only Exp:** Thyroid: **0:83 ppm:**↑ follicular cell hyperplasia **(58% vs 2% in control ♂, ♀: 16% vs 4% in control)** , adenomas **0-250 ppm**: follicular cell carcinomas, ♂ appear more sensitive. Some carcinomas invaded the adjacent parenchyma and/or esophagus and trachea, and two metastasized to the lungs. Thyroid tumour incidence in adult-only exposure was (1/49, 12/46, 37/50 for males and 3/50, 7/44, 30/49 at 0, 83 and 250 ppm, resp) **Combined Perinatal-Adult Exp:** Thyroid: **90-83 and 90-250 ppm**: ↑ follicular cell hyperplasia (♂), this was greater than that observed at 0-83 ppm, indicating some type of perinatal action. There was a similar effect with follicular adenomas/carcinomas. For males, tumour incidence was as follows: 3/46, 14/47, 13/50 and 48/50 for 9:25, 30:83, 90:83 and 90:250 ppm exposures, resp. Other Organs: **90-83 and 90-250 ppm**: ↑ neoplasms of the Zymbal's gland and mononuclear cell leukaemia.	
Smith (1984). **ETU**: thyroid function in two groups of exposed workers. Brit J of Ind Med 41:362-366. PMRA # 1570247	Clinical examinations and thyroid function tests were carried out over a period of 3 years in the UK on 8 workers involved in the manufacture of ETU (average exposure of 10 years) and 5 workers involved in mixing of ETU with rubber (average exposure of 3 years). All subjects were ♂ and ranged from 26-62 years. In the manufacturing group, a personal sampler noted ETU levels of 330 ug/m3 (background levels of 10-240 ug/m3). The mixture group recorded levels of 120-160 ug/m3. Results showed that mixers had significantly lower levels of T4 in their blood compared to controls. No effects were found on TSH or thyroid binding globulin. Although the authors concluded that there was no evidence that thyroid function was severely altered at these dose levels, the T4 results could be accounted for by the exposure scenario of the mixers.		

<table>
<tr><th>Study/Species/ # of animals per group</th><th>Dose Levels/Purity of Test Material</th><th>NOAEL (mg/kg bw/day)</th><th>Results/Effects</th></tr>
<tr><td colspan="4">Reproductive and Developmental Toxicity Studies</td></tr>
<tr><td>2-generation
Rats - SD

25/sex/dose

PMRA # 1570238</td><td>0, 2.5, 25 and 125 ppm

Purity: 98%</td><td>Potential NOAELs (ppm):

<u>Parental</u>
2.5

<u>Offspring</u>
25

<u>Reproductive</u>
125</td><td><u>Parental</u>
≥25 ppm: follicular cell (thyroid) hypertrophy and hyperplasia; ↑ pituitary hypertrophy (♂).
125 ppm: F1 generation had ↓ colloid in the thyroid. The pituitary of the adults had an ↑ in the incidence and severity of anterior cell hypertrophy and the ♂ also had ↑ cellular vacuolization.

<u>Offspring</u>
125 ppm: F0 pups: ↑ mortality lactation days 1-4.

NOAELs on a mg/kg bw basis could not be determined because of stability problems with the test material, unknown feed consumption, and missing pups.

Study considered supplemental</td></tr>
<tr><td>2-phase Reproductive toxicity
Rats, Fischer
Mice, C57BL/6N

Depending on the test, animal numbers ranged from 3-5 per group/litter.

PMRA # 1619136</td><td>Rats: 0, 8, 25, 83, and 250 ppm
(0, 0.8, 2.5, 8.3, 25 mg/kg bw/d)

Mice: 0, 33, 100, 333 and 1000 ppm
(0, 5, 15, 50, 150 mg/kg bw/d)

Purity: 96.7%</td><td colspan="2">Phase I: ♀ dosed before breeding to untreated ♂, then during gestation.
Phase II: weanlings dosed for 9 wks.
<u>Rats</u>
All treatment groups: Dams ↓ bwg, thyroid hyperplasia in both sexes
≥8.3 mg/kg bw/d: ↑ thyroid adenomas (♂), ↓ bwg in weanling ♂.
25 mg/kg bw/d: ♂: ↓ fc and ↑ pituitary vacuolization. Pups: ↓ survival (pnd 4).
<u>Mice</u>
↓ fertility or no pregnancy.
≥50 mg/kg bw/d: ↓ bw in weanlings.
150 mg/kg bw/d: From initial breeding, thyroid hyperplasia and cellular alteration of hepatocytes (cytomegaly, karyomegaly). ♀: ↓ bw during lactation, pups surviving to day 28 had ↓ bw.

NOAELs not set because of low animal numbers.

Study considered supplemental</td></tr>
<tr><td>Developmental, gavage
Rat, Wistar

10-17/dose

PMRA # 1805649, 1805557</td><td>0, 5, 10, 20, 40 mg/kg bw/d, Grp II also treated with 80 mg/kg bw/d

Purity: 100%

Published Papers (1973)</td><td><u>Maternal</u>
40

<u>Developmental</u>
5

Sensitivity

Used for ARfD, acute, short and intermediate dermal and inhalation exposure, and aggregate acute and short-term exposure (females 13+)</td><td>Grp I dams treated 21-42 days before conception, then until gd 15. Other dams dosed gd 6-15 (Grp II) or 7-20 (Grp III).
<u>Dams</u>
80 mg/kg bw/d: lethal to 9/11 dams.
<u>Fetal</u>
≥5 mg/kg bw/d: ↑ in delayed ossification of the parietal bone (grps I and II).
≥10 mg/kg bw/d: (all grps): ↑ meningoencephalocele, meningorrhagia, meningorrhea, hydrocephalus, obliterated neural canal, abnormal pelvic limb posture with equinovarus, and short or kinked tail.
≥40 mg/kg bw/d: retarded growth</td></tr>
</table>

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Developmental, gavage Rats, SD n=6 Acute dose (gd 15) PMRA # 1805524	0, 15, 30, 45 mg/kg bw on gd 15	Pups from each dose group were imaged serially on PND 6, 13, 17 and 27, in order to determine the progression in severity of hydrocephalus. Litter mates were imaged (MRI) on these days and then killed. Hydrocephalus was noted in the images from all animals of the **30 and 45 mg/kg bw** dose levels on PND 6. At this time, the lateral ventricles were dilated less than 1 mm. Hydrocephalus became more severe and by 4 wks of age, all the pups in the high- and about ½ of the mid-dose group had died. Surviving pups of the mid-dose group brains were severely hydrocephalic, with little cortex remaining. In all cases, the MRI corresponded precisely with the brain anatomy observed after termination.	
Gavage Rats, Wistar females PMRA # 1805635	0, 15, 30 mg/kg bw, single dose on gd 13	Histologic study revealed the presence of karyorrhexis in the germinal layer of basal lamina of CNS extending from the thoracid spinal cord to the telencephalon 12h after treatment with **30 mg/kg bw**. At 48h, the spinal cord showed obliteration and duplication of the central canal and disorganization of germinal and mantle layers. In the brain, the ventricular lining was focally denuded, neuroepithelial cells were arranged in the form of rosettes and the nerve cell proliferation was disorganized. In the **15 mg/kg bw** group, cellular necrosis was less severe and consisted of degeneration in a single or a small group of cells widely dispersed in the germinal layer of neuraxis. The initial degenerative changes were observed in a specific nerve cell type, identified as the undifferentiated migrating neuroblast.	
Developmental, gavage Rats, SD 22/dose gd 6-20 PMRA # 1805574	0, 15, 25, 35 mg/kg bw/d	Maternal 35 Developmental 15 **Sensitivity**	Dams No maternal toxicity noted. Fetal **≥25 mg/kg bw/d**: ↑ dilated brain ventricles (33.5%). **35 mg/kg bw/d**: ↑ cranial meningocele and meningorrhea, severe hindlimb talipes, hydroureter and dilated ureter, and ↓ ossification of skull bones. 43.5% of fetuses had short or kinky tails, 93% had ELV, 33.5% had dumbell-shaped or bilobed vertebral centra.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Developmental Mancozeb/ETU Rats, albino 26/dose gd 6-15 PMRA # 1651466	Mancozeb: 0, 2, 8, 32, 128 or 512 mg/kg bw/d Purity: 83% ETU: 50 mg/kg bw/d Purity: 99%	Mancozeb Maternal 32 Developmental 128 ETU None set.	**Mancozeb** Maternal: **≥128 mg/kg bw/d**: ↓ fc on days 10-15, bw on gd 20 and bwg throughout **512 mg/kg bw/d**: 1 death due to treatment, 2 sacrificed due to abortion, lethargy, scruffy coat, and diarrhea. Developmental: **512 mg/kg bw/d**: gross dev defects, CNS defects, skeletal defects, cryptorchidism, abortions, ↑ resorptions, ↓ fetal bw. **ETU** Maternal: ↓ bwg (does not appear to be corrected) Developmental: gross dev defects, CNS defects, skeletal defects, cryptorchidism, ↓ fetal bw, exencephaly, ectorpic kidneys, agenesis of kidneys, hydronephrosis, reduced stomach, edematour fat pads, less than 13 ribs, fused lumbar, sacral or caudal vertebrae, oligodactyl, syndactyl, webbed digits, anal atresia. Comment: Although mancozeb and ETU caused many of the same dev effects (except total resorptions), ETU was a more severe dev toxicant for the following reasons: 1) < ETU caused the effects 2) dev defects occurred with ↑ freq 3) more types of dev defects 4) all defects occurred with MINIMAL to NO maternal toxicity.
Developmental, dermal Rats, SD PMRA # 1805579	0, 25, 50 mg/kg bw/d in DMSO gd 10-11. or 50 mg/kg bw/d gd 12-13 Purity: 98%	Potential LOAEL of 50, gd 12-13	gd 10-11: **50 mg/kg bw/d**: short tails (3/83 pups), fused ribs (2/83 pups). gd 12-13: **50 mg/kg bw/d:** fetal deformities in all offspring: encephalocele, part or entire tail missing, missing leg bones, hunchback curvature of the spine, short mandible, fused ribs and sternebrae.
Developmental, dermal Rat, SD albino PMRA # 1619154	100 mg/kg bw/d on gd 12 & 13 50 and 100 mg/kg bw/d on gd 10 & 11		gd 12-13: **100 mg/kg bw/d**: no maternal effects or embryo-mortality. All 73 fetuses demonstrated marked skeletal malformations. gd 10-11: **50 and 100 mg/kg bw/d**: slight ↑ in skeletal malformations.
Special Developmental Rats Single oral dose on gd 15 PMRA # 1805559	0, 15, 30 or 45 mg/kg bw/d	Potential NOAEL of 15	Pups **≥30 mg/kg bw/d**: ↑ hydrocephalus, microphtalmia and mortality. Hydrocephalic condition accompanied by atrophy of the cerebral cortex and subcortical white matter. Surviving pups had motor defects and dome-shaped head. A cross-fostering study of survivors found that developmental toxicity was due to in utero exposure and not to exposure in milk.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Developmental, gavage Rabbits, NZW 5-7 dams/dose gd 7-20 PMRA # 1805557	0, 5, 10, 20, 40 or 80 mg/kg bw/d Purity: 100%	Maternal: >80 Developmental 40 Sensitivity at high doses compared to rat	Not maternal tox Developmental **80 mg/kg bw/d**: ↑ resorption sites, degeneration of proximal convoluted tubules in the kidney and ↓ brain wt. Low animal numbers and lack of detailed reporting. **Study considered supplemental**
Developmental, gel cap Cats - European and Persian 7-14/dose PMRA # 1805550, 1805636	0, 5, 10, 30, 60 mg/kg bw/d days 16-35 or 120 mg/kg bw days 16-34. Purity: ?	Potential maternal 5 Potential developmental 10	Maternal **≥10 mg/kg bw/d**: ↑ ataxia, tremors, hindlimb paralysis, mortality **≥30 mg/kg bw/d**: no cats survived. Developmental 11/35 fetuses obtained from 6 cats killed in a moribund state (4 from 30 mg/kg bw/d, 1 each from 60 and 120 mg/kg bw/d) were malformed with coloboma, cleft palate, spina bifida, umbilical hernia etc. ETU rapidly metabolizes to S-methyl ETU in cats, but not in rats. May explain why developmental effects in rat are at non-maternally toxic doses, but in the cat developmental effects are at maternally toxic dose.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Special Study using maneb, ETU and EBIS; gastric intubation Mice, CD1 Rats, SD Hamsters, Golden Guinea pigs, Hartley PMRA # 1805604	**Dosing** **Rats:** maneb (0, 120, 240 and 480 mg/kg bw/d, gd 7-16) ETU (0, 5, 10, 20, 30, 40, 80 mg/kg bw/d, gd 7-21) EBIS (0, 7.5, 25, 30 mg/kg bw/d, gd 7-21) **Mice:** maneb (0, 375, 750, 1500 mg/kg bw/d, gd 7-16) ETU (0, 100, 200 mg/kg bw/d, gd 7-16) EBIS (0, 50, 100, 200 mg/kg bw/d, gd 7-16) **Hamster:** ETU (0, 25, 50, 100 mg/kg bw/d, gd 5-10) **Guinea Pigs:** ETU (0, 50, 100 mg/kg bw/d, gd 7-25)	Animals for postnatal study were allowed to litter and culled to 4/sex and weaned on day 22 postpartum. **For ETU, no devel effects in mouse, hamster or guinea pig, even at dose levels producing malformations in 100% of the rat pups.** Appears maneb produces paralytic effect through metabolic conversion to EBIS, and teratogenic effects through conversion to ETU. Lack of terato of EBIS may be that less compound is needed to produce paralysis than for metabolic conversion to sufficient quantities of ETU. There is a steep dose-response with regard to dev tox of ETU in rat. **ETU Dev NOAEL = 5 mg/kg bw/d** **Thus far, there is nothing to indicate that humans would be less sensitive than the rat to the developmental effects of ETU.**	**Maneb**: maternal *rats*: ↓ bwg, ↑ rel liver wt (dose-related manner). **480 mg/kg bw/d**: ↓ fetal bw, caudal ossification and ↑ hydrocephalus. Maternal *mice*, **≥375 mg/kg bw/d:** ↑ rel liver wt and Compound-induced paralysis. Fetuses had ↓ caudal ossification. **EBIS:** no fetal effects, maternal *rats* had ↓ bwg at **30 mg/kg bw/d**. Amount admin limited by compound-induced paralysis in dams. **ETU**: no apparent effects in *hamsters* or *guinea pigs*. *Rats*: Maternal: **80 mg/kg bw/d**: ↓ bwg and 25% mortality. DEV: **≥10 mg/kg bw/d**: ↓ bw **≥20 mg/kg bw/d**: ↑ hydrocephalus **≥40 mg/kg bw/d**: ↓ ossification, ↑ encephalocele, kyphosis and digit defects. **80 mg/kg bw/d**: ↑ mortality, edema, gross defects of the skeletal system and CNS. *Mice*: Maternal: ↑ rel liver wt (**≥100 mg/kg bw/d**). @ **200 mg/kg bw/d,** fetuses had ↑ # of supernumerary ribs. Post-natal results: **Maneb**: ♂ had a delay in eye opening **EBIS**: delayed eye opening, (♀) ↓ bw **ETU**: there were no apparent differences reported in open field activity between ♂ fetuses surviving the high dose with hydrocephalus and their apparently normal mates.
Special Study, gavage Mice, JCL-ICR Rats, Wistar Hamsters, Golden dosed during organogenesis PMRA # 1805594	Rats: 0, 10, 20, 30, 40, 50 mg/kg bw/d Mice: 0, 200, 400, 800 mg/kg bw/d Hamsters: 0, 90, 270, 810 mg/kg bw/d	No maternal toxicity in any of 3 species Developmental: Rats: 20 (JMPR), <10 (EPA and PMRA) Mice: >800 Hamsters: 90	**Rats**: **≥10 mg/kg bw/d**: ↑ dilation of the lateral 4th ventricle (2 %) - this instance is within older historical controls, however a previous reported study indicates severe head malformations at this dose and that result takes precedence in the overall assessment. **≥20 mg/kg bw/d**: ↑ dilation of the lateral 4th ventricle (39%) **≥30 mg/kg bw/d**: ↓ mean fetal bw, short kinky tail, curved clavicles **≥40 mg/kg bw/d**: meningocele (66%), fused/wavy ribs, fused sternebrae, malformed vertebrae and scholiosis. **Mice**: No toxicity noted **Hamsters**:**≥270 mg/kg bw/d**: ↓ ♀ fetal bw, ↑ malformed lumbar and sacral vertebrae. **810 mg/kg bw/d**: dilation of the lateral 4th ventricle, ↑ cleft palate, short/kinky tail, oligodactyly.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Liver enzymatic assays, gavage Mice, Swiss albino Rats, Wistar 8 ♂ mice 8 ♂ rats PMRA # 1805566	ETU (98% pure): 0, 100 or 200 mg/kg bw.	**ETU** causes a dose-dependent ↓ of aminopyrine-N-demethylase in rats, but did not modify this activity in mice. ETU did not affect aniline hydroxylase activity in rats, but caused a 2X ↑ in mice. The study authors concluded that qualitatively different responses of hepatic microsomal enzymes may be partially responsible for the differences in acute toxicity and teratogenicity demonstrated in rats and mice.	
Further Comparison of rat and mouse teratogenicity PMRA # 1805569	The ½ life and ↑ metabolism of ETU in the mouse compared with the rat may be partly responsible for the differences in teratogenic response between the 2 species. After 48 hrs, the total amount of ETU excreted is similar between the 2 species, but the radioactive label is still detected in all tissues in the rat, but only in the liver of the mouse. Material excreted in the urine indicated that 95% appeared as ETU in the rat, but only 40% of the material was unchanged ETU in the mouse. However, the following results confuse the issue: 1) a dose 10X that produced hydrocephalus in rat fetuses had no effect on mouse development. 2) the rat and guinea pig have similar excretion patterns and ETU is not teratogenic in the guinea pig. Thus, metabolism and rapid elimination of ETU in the mouse may assist in averting teratogenic effects in this species, but it is not the only factor leading to this ↓ sensitivity. The fact that ETU is only detected in the mouse liver may be related to the carcinogenicity that forms there.		
Developmental, gavage Rats, SD Rats were hypothyroid and euthyroid 10-12/dose PMRA # 1805624	40 mg/kg bw, days 7-15 of gestation. Purity: 100%	Rats were given thyroxine to determine if ETU terato occurred through alterations of maternal thyroid function. ETU was determined to be a teratogen, but not directly through alterations of maternal thyroid status. In other words, the thyroid alterations enhanced the developmental toxicity of ETU, but were not the primary factor. -ETU lowered serum T_4 - ↓T_4 alone was embryotoxic, but not teratogenic -hypothyroidism altered the spectrum of malformations in response to ETU both quantitatively and qualitatively.	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Genotoxicity Studies			
ETU has about 100 genotoxicity studies in the database. Also overviews of the genetic data are available (EPA, IARC). The USEPA has determined that ETU is weakly genotoxic and IARC states it is not genotoxic. General overview: **Salmonella reversion assays**: 10 positive; 5 negative **e-coli**: 1 positive; 2 negative **Mammalian gene mutation assay**: 1 positive; 2 negative **Sex-linked recessive lethal:** 2 negative; 2 inconclusive **Forward mutation**: negative (all) **In vitro chromosomal aberrations**: 3 negative; 1 positive **Micronucleus assay:** 2 positive; 5 negative **Dominant lethal:** 1 positive; 2 negative **Reciprocal assay:** 2 positive; 4 negative **In vitro Unscheduled DNA synthesis:** 1 positive with activation; 4 negative **Sister Chromatid Exchange in vitro:** 5 negative **Sister Chromatid Exchange in vivo:** 1 negative **Mitotic gene conversion:** 3 positive; 3 negative Numerous other studies with a equivocal results for differential killing, and negatives for cell transformation and spermhead abnormalities tests. The PMRA concurs with the USEPA, ETU has weak genotoxic potential. PMRA # 1805544, 1570258, 1805578			

Table 3 Toxicology Endpoints for the Health Risk Assessment for Metiram

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	CAF or MOE[1]
Acute Reference Dose Females 13-49	Post-implantation Loss	Rat Developmental Toxicity	NOAEL 80	1000
Acceptable Daily Intake	Thyroid and Thyroid Hormones	One Year Dog Toxicity	NOAEL 2.5	1000
Short-term Dermal [2]	Occupational			
	Neuromuscular Effects	90-day Neurotoxicity in Rats	NOAEL 6.7	1000
Intermediate Dermal	Occupational			
	Thyroid and Thyroid Hormones	One Year Dog Toxicity	NOAEL 2.5	1000
Short, and Intermediate Inhalation	Occupational			
	Decreased Body Weight	90-day Inhalation Toxicity in Rat	NOAEL 0.5	1000

[1] MOE refers to target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 7% is used in a route-to-route extrapolation for metiram.

Table 4 Toxicology Endpoints for the Health Risk Assessment for ETU

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	CAF or MOE[1]
Acute Reference Dose Females 13-49	Malformations	Developmental rat	5 mg/kg bw/day NOAEL	1000
Acute Reference Dose Gen Pop	N/A			
Chronic Dietary	Body weight and thyroid	One year dog	0.18 mg/kg bw/day NOAEL	300
Acute, Short-, and Intermediate- term Dermal[2] and Inhalation[3]	**Occupational**			
	Malformations	Developmental rat	5 mg/kg bw/day NOAEL	1000
Long-term Dermal[2] and Inhalation[3]	**Occupational**			
	Bodyweight and thyroid	One year dog	0.18 mg/kg bw/day NOAEL	300
Acute and short-term, Females 13-49	**Aggregate**			
	Malformations	Developmental rat	5 mg/kg bw/day NOAEL	1000
Short-term, General population	**Aggregate**			
	Thyroid effects	90-day mouse	1.7 mg/kg bw/day NOAEL	300
Cancer Risk	Fetal malformations q_1^* of 0.0601 (mg/kg bw/day)$^{-1}$	Based on incidences of liver tumours in a combined chronic/carcinogenicity/reproduction study		

[1] CAF (Composite assessment factor) refers to the total of uncertainty and PCPA factors for dietary risk assessments, MOE refers to target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 45% is used in a route-to-route extrapolation.

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) is used in route-to-route extrapolation.

Appendix V Agricultural Mixer/Loader/Applicator and Post-Application Risk Assessment

Table 1 Dermal and Inhalation MOEs for Short-to-Intermediate Term Mixing/Loading and Applying Metiram

Crop	Application Equipment	Formulation	Max Rate	Area Treated	Daily Exposure µg/kg bw/day		Margins of Exposure		Kg ai Handled/Day to Achieve Target MOE^{E}
					Dermal^{A}	Inhalation^{B}	Dermal^{C}	Inhalation^{D}	
Label PPE: Open mix/load, open cab airblast. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves.									
Apple	Airblast	WDG	4.8 kg ai/ha	16 ha	55.72	7.48	**120**	**67**	5
Engineering Controls: Mid-Level PPE (coveralls over long sleeves and long pants, and chemical-resistant gloves), closed mixing/loading, and closed cab.									
Apple	Airblast	WDG	4.8 kg ai/ha	16 ha	3.58	0.83	1872	**600**	45
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Asparagus, Celery, Tomato	Groundboom – Farmer/Custom	WDG	2.6 kg ai/ha	30 ha	15.35	2.21	**437**	**227**	20
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves (except during application), closed mixing and loading, and open cab. Applicators must also wear a respirator.									
Asparagus, Celery, Tomato	Groundboom – Farmer/Custom	WDG	2.6 kg ai/ha	30 ha	2.26	0.31	2966	1626	N/A
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Carrot	Groundboom – Farmer/Custom	WDG	1.8 kg ai/ha	30 ha	10.62	1.53	**631**	**327**	20
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves (except during application)), closed mixing and loading, and open cab. Applicators must also wear a respirator.									
Carrot	Groundboom – Farmer/Custom	WDG	1.8 kg ai/ha	30 ha	1.56	0.21	4284	2348	N/A
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Grapes	Airblast	WDG	1.6 kg ai/ha	16 ha	18.57	2.49	**361**	**200**	5
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves), closed mixing and loading, and closed cab.									
Grapes	Airblast	WDG	1.6 kg ai/ha	16 ha	1.19	0.28	5617	1799	N/A
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Sugar Beets, Potatoes	Groundboom – Farmer	WDG	1.8 kg ai/ha	100 ha	35.41	5.09	**189**	**98**	20
	Groundboom -	WDG	1.8 kg	300 ha	106.25	15.27	**63**	**33**	20

Table 1 Dermal and Inhalation MOEs for Short-to-Intermediate Term Mixing/Loading and Applying Metiram

Crop	Application Equipment	Formulation	Max Rate	Area Treated	Daily Exposure µg/kg bw/day		Margins of Exposure		Kg ai Handled/Day to Achieve Target MOE[E]
					Dermal[A]	Inhalation[B]	Dermal[C]	Inhalation[D]	
	Custom		ai/ha						
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves (except during application), closed mixing and loading, and open cab. Applicators must also wear a respirator.									
Sugar Beets, Potatoes	Groundboom – Farmer	WDG	1.8 kg ai/ha	100 ha	5.21	0.71	1285	**705**	125
	Groundboom - Custom	WDG	1.8 kg ai/ha	300 ha	15.64	2.13	**428**	**235**	125
Label PPE: Open Mix/load. M/L wearing coveralls over long-sleeved shirt and long pants, and chemical-resistant gloves. Applicators wearing long-sleeved shirt and long pants, and chemical-resistant gloves.									
Potatoes	Aerial – Mix/Load	WDG	1.8 kg ai/ha	400 ha	66.20	10.49	**101**	**48**	34.31
	Aerial - Applicator	WDG	1.8 kg ai/ha	400 ha	6.96	0.72	**963**	**694**	500.00
Engineering Controls: Mid-Level PPE (coveralls over long sleeves and long pants, and chemical-resistant gloves), and closed mixing and loading.									
Potatoes	Aerial – Mix/Load	WDG	1.8 kg ai/ha	400 ha	6.62	1.85	1012	**270**	194.44

Shaded cells indicate that MOEs are less than the target, WDG = Water Dispersible Granules

[A] Where dermal exposure µg/kg bw/day = (unit exposure (PHED) × area treated per day × use rate × 7% dermal absorption)/70 kg bw

[B] Where the inhalation exposure µg/kg bw/day = (unit exposure (PHED) × area treated per day × use rate)/70 kg bw

[C] Based on the short-to-intermediate term oral NOAEL of 6.7 mg/kg bw/day from the 90-day neurotoxicity study, target MOE of 1000.

[D] Based on the short-to-intermediate term NOAEL of 0.5 mg/kg bw/day from the 90-day inhalation study, target MOE of 1000.

[E] Calculated using the following formula: (target dermal (0.0067 mg/kg bw/day) or inhalation (0.0005 mg/kg bw/day) exposure/unit exposure (µg/kg ai handled) × 7% dermal absorption (if applicable) × 70 kg bw × conversion factor (1000 µg/mg)

Table 2 Dermal and Inhalation Short-to-Intermediate Term MOEs for ETU from Mixing/Loading and Applying Metiram

Crop	Application Equipment	Formulation	Max Rate	Area Treated	Daily Exposure µg/kg bw/day			Total Exposure to ETU (µg/kg bw/day)^{D}	MOE^{E}
					ETU in Tank Mix		Metabolic Conversion from MET^{C}		
					Dermal^{A}	Inhalation^{B}			
Label PPE: Open mix/load, open cab airblast. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves.									
Apple	Airblast	WDG	4.8 kg ai/ha	16 ha	3.58×10^{-1}	7.48×10^{-3}	4.74	5.11	**979**
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves), closed mixing and loading, and closed cab.									
Apple	Airblast	WDG	4.8 kg ai/ha	16 ha	2.30×10^{-2}	8.34×10^{-4}	3.31×10^{-1}	3.55×10^{-1}	14095
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves), closed mixing and loading, and closed cab. Restrictions on area treated per day (45 kg ai/day, approx. 9.5 ha at 4.8 kg ai/ha)									
Apple	Airblast	WDG	4.8 kg ai/ha	9.5 ha	1.37×10^{-2}	4.95×10^{-4}	1.96×10^{-1}	2.11×10^{-1}	23739
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Asparagus, Celery, Tomato	Groundboom – Farmer/Custom	WDG	2.6 kg ai/ha	30 ha	9.87×10^{-2}	2.21×10^{-3}	1.32	1.42	3528
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves (except during application)), closed mixing and loading, and open cab. Applicators must wear a respirator.									
Asparagus, Celery, Tomato	Groundboom – Farmer/Custom	WDG	2.6 kg ai/ha	30 ha	1.45×10^{-2}	3.08×10^{-4}	1.92×10^{-1}	2.07×10^{-1}	24118
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Carrot	Groundboom - Farmer	WDG	1.8 kg ai/ha	30 ha	6.83×10^{-2}	1.53×10^{-3}	9.11×10^{-1}	9.81×10^{-1}	5096
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves (except during application)), closed mixing and loading, and open cab. Applicators must wear a respirator.									
Carrot	Groundboom - Farmer	WDG	1.8 kg ai/ha	30 ha	1.01×10^{-2}	2.13×10^{-4}	1.33×10^{-1}	1.44×10^{-1}	34838
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Grapes	Airblast	WDG	1.6 kg ai/ha	16 ha	1.19×10^{-1}	2.49×10^{-3}	1.58	1.70	2938
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves), closed mixing and loading, and closed cab.									
Grapes	Airblast	WDG	1.6 kg ai/ha	16 ha	7.67×10^{-3}	2.78×10^{-4}	1.10×10^{-1}	1.18×10^{-1}	42286
Label PPE: Open mix/load, open cab groundboom. M/L/A wearing a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application).									
Sugar Beets, Potato	Groundboom - Farmer	WDG	1.8 kg ai/ha	100 ha	2.28×10^{-1}	5.09×10^{-3}	3.04	3.27	1529
	Groundboom - Custom	WDG	1.8 kg ai/ha	300 ha	6.83×10^{-1}	1.53×10^{-2}	9.11	9.81	**510**
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application), closed mixing and loading, and open cab. Applictors must wear a respirator.									
Sugar Beets, Potatoes	Groundboom - Farmer	WDG	1.8 kg ai/ha	100 ha	3.35×10^{-2}	7.10×10^{-4}	4.44×10^{-1}	4.78×10^{-1}	10451
	Groundboom - Custom	WDG	1.8 kg ai/ha	300 ha	1.01×10^{-1}	2.13×10^{-3}	1.33	1.44	3484

Crop	Application Equipment	Formulation	Max Rate	Area Treated	Daily Exposure µg/kg bw/day			Total Exposure to ETU (µg/kg bw/day)[D]	MOE[E]
					ETU in Tank Mix		Metabolic Conversion from MET[C]		
					Dermal[A]	Inhalation[B]			
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application), closed mixing and loading, and open cab. Applicators must wear a respirator. Restriction on area treated per day (125 kg ai/day, approx. 70 ha at 1.8 kg ai/ha).									
Sugar Beets, Potatoes	Groundboom	WDG	1.8 kg ai/ha	70 ha	2.35×10^{-2}	4.97×10^{-4}	3.11×10^{-1}	3.35×10^{-1}	14930
Label PPE: Open mix/load. M/L wearing coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves. Applicators wear long-sleeved shirt, long pants, and chemical-resistant gloves.									
Potato	Aerial – Mix/Load	WDG	1.8 kg ai/ha	400 ha	4.26×10^{-1}	1.05×10^{-2}	5.75	6.19	**808**
	Aerial - Applicator	WDG	1.8 kg ai/ha	400 ha	4.47×10^{-2}	7.20×10^{-4}	5.76×10^{-1}	6.21×10^{-1}	8051
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves), closed mixing and loading.									
Potato	Aerial – Mix/Load	WDG	1.8 kg ai/ha	400 ha	4.26×10^{-2}	1.85×10^{-3}	6.35×10^{-1}	6.80×10^{-1}	7356
Engineering Controls: Mid-Level PPE (coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves), and closed mixing and loading. Applicators wear long-sleeved shirt, long pants, and chemical-resistant gloves. Restrictions on area treated per day (195 kg ai/day, approx. 110 ha at 1.8 kg ai/ha).									
Potato	Aerial – Mix/Load	WDG	1.8 kg ai/ha	110 ha	1.17×10^{-2}	5.09×10^{-4}	1.75×10^{-1}	1.87×10^{-1}	26748
	Aerial - Applicator	WDG	1.8 kg ai/ha	110 ha	1.23×10^{-2}	1.98×10^{-4}	1.58×10^{-1}	1.71×10^{-1}	29275

Shaded cells indicate MOEs that are less than the target, WDG = water dispersible granules

[A] Where dermal exposure µg/kg bw/day = (unit exposure (PHED) × area treated per day × use rate × 45% dermal absorption)/70 kg bw

[B] Where inhalation exposure µg/kg bw/day = (unit exposure (PHED) × area treated per day × use rate)/70 kg bw

[C] Systemic exposure µg/kg bw/day = total exposure to metiram (as expressed in Appendix II - Table 1, dermal exposure + inhalation exposure) × metabolic conversion of metiram to ETU (7.5%).

[D] Total daily exposure to ETU µg/kg bw/day = Sum of daily exposure to ETU from tank mix (dermal exposure + inhalation exposure) and metabolic conversion of ETU.

[E] Based on the short-to-intermediate term NOAEL of 5 mg/kg bw/day, target MOE of 1000.

Table 3 ETU Cancer Exposure and Risk Estimates for Occupational Handlers

Crop	Formulation / Application Method	Rate	Applicator	Area Treated	Absorbed Daily Dose (µg/kg bw/day)[A]	Lifetime Average Daily Dose (mg/kg bw/day)[B]	Cancer Risk[C]
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves), closed mixing and loading, and closed cab. Restrictions on area treated per day (45 kg ai/day, approx. 9.5 ha at 4.8 kg ai/ha).							
Apple	WDG/Airblast	4.8 kg ai/ha	Farmer	9.5 ha	2.11×10^{-1}	1.23×10^{-6}	7×10^{-8}
	WDG/Airblast	4.8 kg ai/ha	Custom	9.5 ha	2.11×10^{-1}	9.23×10^{-6}	6×10^{-7}
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application)), closed mixing and loading, and open cab. Applicators must wear a respirator.							
Asparagus, Celery, Tomato	WDG/Groundboom	2.6 kg ai/ha	Farmer	30 ha	2.07×10^{-1}	1.21×10^{-6}	7×10^{-8}
	WDG/Groundboom	2.6 kg ai/ha	Custom	30 ha	2.07×10^{-1}	9.09×10^{-6}	5×10^{-7}
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application)), closed mixing and loading, and open cab. Applicators must wear a respirator.							

Crop	Formulation / Application Method	Rate	Applicator	Area Treated	Absorbed Daily Dose (µg/kg bw/day)[A]	Lifetime Average Daily Dose (mg/kg bw/day)[B]	Cancer Risk[C]
Carrot	WDG/Groundboom	1.8 kg ai/ha	Farmer	30 ha	1.44×10^{-1}	8.39×10^{-7}	5×10^{-8}
	WDG/Groundboom	1.8 kg ai/ha	Custom	30 ha	1.44×10^{-1}	6.29×10^{-6}	4×10^{-7}
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves), closed mixing and loading, and closed cab.							
Grape	WDG/Airblast	1.6 kg ai/ha	Farmer	16 ha	1.18×10^{-1}	5.18×10^{-7}	3×10^{-8}
	WDG/Airblast	1.6 kg ai/ha	Custom	16 ha	1.18×10^{-1}	5.18×10^{-6}	3×10^{-7}
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves (except during application)), closed mixing and loading, and open cab. Applicators must wear a respirator. Restrictions on area treated per day (125 kg ai/day, approx. 70 ha at 1.8 kg ai/ha).							
Sugar Beets, Potatoes	WDG/Groundboom-Sugar Beets	1.8 kg ai/ha	Farmer	70 ha	3.35×10^{-1}	9.79×10^{-7}	6×10^{-8}
	WDG/Groundboom - Potatoes	1.8 kg ai/ha	Farmer	70 ha	3.35×10^{-1}	4.89×10^{-6}	3×10^{-7}
	WDG/Groundboom	1.8 kg ai/ha	Custom	70 ha	3.35×10^{-1}	1.47×10^{-5}	9×10^{-7}
Engineering Controls: Mid-Level PPE (coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves), and closed mixing and loading. Applicators wear a long-sleeved shirt, long pants, and chemical-resistant gloves. Restrictions on area treated per day (195 kg ai/day, approx. 110 ha at 1.8 kg ai/ha).							
Potato	WDG/Aerial	1.8 kg ai/ha	Mix/Load	110 ha	1.87×10^{-1}	8.19×10^{-6}	5×10^{-7}
	WDG/Aerial	1.8 kg ai/ha	Applicator	110 ha	1.71×10^{-1}	7.49×10^{-6}	5×10^{-7}

Shaded cells indicate cancer risk greater than 1×10^{-5}, WDG = Water Dispersible Granules

[A] Represents total daily exposure to ETU expressed in µg/kg bw/day, as presented in Appendix II, Table 2.

[B] Calculated using the following formula:

$$\frac{\text{Absorbed Daily Dose (mg/kg bw/day)} \times \text{Treatment Frequency (days per year)} \times \text{Working Duration (40 yrs)}}{\text{365 days/yrs} \times \text{Life Expectancy (75 yrs)}}$$

Treatment frequency for farmer applicators was assumed to be equal to the maximum number of applications and ranged from 2-10 days per year. It was assumed that custom applicators would be exposed for 30 days per year.

[C] Calculated using the following formula: LADD (mg/kg bw/day) × q_1* $(0.0601 \text{ mg/kg bw/day})^{-1}$

Table 4 Restricted Entry Interval for Commercial Post-Application Activities for Metiram

Crop	Rate (kg ai/ha)	Activity	TC (cm^2/hr)	Target Residue Limit (µg/cm^2)[A]	Margin of Exposure (Day 0)[B]	Restricted Entry Interval (days)[C]
Apples	4.8	Thinning	3000	0.2792	**18**	>170
		Hand Harvesting	1500	0.5583	**36**	146
		Hand Line Irrigation	1100	0.7614	**50**	132
		Pruning/Scouting	500	1.6750	**109**	98
		Hand Weeding	100	8.3750	**545**	27
Asparagus	2.6	Scouting/Irrigation	500	1.6750	**201**	71
		Hand Weeding	100	8.3750	1007	12 hrs
Celery	2.6	Hand Harvest	2500	0.3350	**40**	142
		Irrigation/Scouting	1500	0.5583	**67**	119
		Hand Weeding	500	1.6750	**201**	71
Tomato	2.6	Hand Harvest	1000	0.8375	**101**	101
		Irrigation/Scouting	700	1.1964	**144**	86
		Hand Weeding	500	1.6750	**201**	71
Carrot	1.8	Hand Harvest	2500	0.3350	**58**	125
		Irrigation/Scouting	300	2.7917	**485**	32
Sugar Beets	1.8	Irrigation/Scouting	1500	0.5583	**167**	79
		Thinning/Hand Weeding	100	8.3750	2511	12 hrs
Potatoes	1.8	Irrigation/Scouting	1500	0.5583	**49**	133
		Thinning/Hand Weeding	300	2.7919	**245**	62
Grapes	1.6	Cane Turning/Girdling	19300	0.0434	**11**	>175
		Hand Harvest	8500	0.0985	**24**	165
		Hand Line Irrigation	1100	0.7614	**184**	75
		Scouting/Hand Weeding	700	1.1964	**290**	55

Shaded cells indicate margins of exposure that are less than the target.

[A] Calculated using the following formula: Target Residue Limit (µg/cm^2) = NOAEL (6.7 mg/kg bw/day) × Body Weight (70 kg) × Conversion Factor (1000 µg/mg)

TC (µg/cm^2) × Duration (8 hrs/day) × Target MOE (1000) × Dermal Absorption (7%)

Target residue limit refers to the residue level required to reach the target MOE.

[B] Calculated using the short-to-intermediate term oral NOAEL of 6.7 mg/kg bw/day from the 90- day neurology study, target MOE of 1000.

[C] Restricted entry interval refers to the day following application when metiram residues are less than the target residue limit or reach the level required for the target MOE.

Table 5 ETU MOEs for Commercial Post-Application Activities for Metiram

Crop	Rate (kg ai/ha)	Activity	TC (cm^2/hr)	MTR REI[A]	ETU MOE[B]		ETU REI[E]
					MTR REI[C]	Day 0[D]	
Apples	4.8	Thinning	3000	>170	1909	**77**	135
		Hand Harvest	1500	146	2492	**154**	98
		Hand Line Irrigation	1100	132	2617	**210**	81
		Pruning/Scouting	500	98	3038	**461**	40
		Hand Weeding	100	27	3902	2306	12 hrs
Asparagus	2.6	Irrigation/Scouting	500	71	3359	**851**	9
		Hand Weeding	100	12 hrs	4256	4256	12 hrs

Crop	Rate (kg ai/ha)	Activity	TC (cm^2/hr)	MTR REI[A]	ETU MOE[B]		ETU REI[E]
					MTR REI[C]	Day 0[D]	
Celery	2.6	Hand Harvest	2500	142	2562	**170**	92
		Irrigation/Scouting	1500	119	2777	**284**	66
		Hand Weeding	500	71	3359	**851**	9
Tomato	2.6	Hand Harvest	1000	101	2968	**426**	44
		Irrigation/Scouting	700	86	3192	**608**	26
		Hand Weeding	500	71	3359	**851**	9
Carrot	1.8	Hand Harvest	2500	125	2694	**246**	73
		Irrigation/Scouting	300	32	3821	2049	12 hrs
Sugar Beets	1.8	Irrigation/Scouting	1500	79	3327	**721**	17
		Thinning/Hand Weeding	100	12 hrs	10822	10822	12 hrs
Potatoes	1.8	Irrigation/Scouting	1500	133	2544	**202**	84
		Thinning/Hand Weeding	300	62	3335	1008	12 hrs
Grapes	1.6	Cane Turning/Girdling	19300	>175	1249	45	163
		Hand Harvest	8500	165	2358	**102**	120
		Hand Line Irrigation	1100	75	3357	**787**	13
		Scouting/Hand Weeding	700	55	3597	1237	12 hrs

Shaded cells are less than the target MOE.

[A] Restricted entry interval refers to the day that workers can enter treated fields, it is the day when metiram residues are less than the target residue limit as presented in Appendix II, Table 4.

[B] Based on the short-to-intermediate term NOAEL of 5 mg/kg bw/day, target MOE of 1000.

[C] Refers to ETU MOE on the REI day required for metiram.

[D] Refers to ETU MOE on day 0, the first day following the maximum number of applications.

[E] Refers to the day that the calculated ETU MOE is greater than the target of 1000.

Table 6 ETU Cancer Risk for Post-Application Workers

Crop	Activity	REI[A]		ETU LADD (mg/kg bw/day)[B]		Cancer Risk[C]	
		Metiram	ETU	Metiram	ETU	Metiram	ETU
Apples	Thinning	>170	135	8.66×10^{-5}	1.66×10^{-4}	5×10^{-6}	1×10^{-5}
	Hand Harvest	146	98	6.72×10^{-5}	1.65×10^{-4}	4×10^{-6}	1×10^{-5}
	Hand Line Irrigation	132	81	6.42×10^{-5}	1.67×10^{-4}	4×10^{-6}	1×10^{-5}
	Pruning/Scouting	98	40	5.51×10^{-5}	1.66×10^{-4}	3×10^{-6}	1×10^{-5}
	Hand Weeding	27	12 hrs	4.27×10^{-5}	7.20×10^{-5}	3×10^{-6}	4×10^{-6}
Asparagus	Irrigation/Scouting	71	9	4.98×10^{-5}	1.64×10^{-4}	3×10^{-6}	1×10^{-5}
	Hand Weeding	12 hrs	12 hrs	1.17×10^{-4}	1.17×10^{-4}	7×10^{-6}	7×10^{-6}
Celery	Hand Harvest	142	92	6.73×10^{-5}	1.67×10^{-4}	4×10^{-6}	1×10^{-5}
	Irrigation/Scouting	119	66	6.04×10^{-5}	1.64×10^{-4}	4×10^{-6}	1×10^{-5}
	Hand Weeding	71	9	4.98×10^{-5}	1.64×10^{-4}	3×10^{-6}	1×10^{-5}
Tomato	Hand Harvest	101	44	5.65×10^{-5}	1.67×10^{-4}	3×10^{-6}	1×10^{-5}
	Irrigation/Scouting	86	26	5.24×10^{-5}	1.65×10^{-4}	3×10^{-6}	1×10^{-5}

Crop	Activity	REI[A]		ETU LADD (mg/kg bw/day)[B]		Cancer Risk[C]	
		Metiram	ETU	Metiram	ETU	Metiram	ETU
	Hand Weeding	71	9	4.98×10^{-5}	1.64×10^{-4}	3×10^{-6}	1×10^{-5}
Carrot	Hand Harvest	125	73	6.23×10^{-5}	1.66×10^{-4}	4×10^{-6}	1×10^{-5}
	Irrigation/Scouting	32	12 hrs	4.36×10^{-5}	8.10×10^{-5}	3×10^{-6}	5×10^{-6}
Sugar Beets	Irrigation/Scouting	79	17	5.03×10^{-5}	1.65×10^{-4}	3×10^{-6}	1×10^{-5}
	Thinning/Hand Weeding	12 hrs	12 hrs	1.53×10^{-5}	1.53×10^{-5}	9×10^{-7}	9×10^{-7}
Potatoes	Irrigation/Scouting	133	84	6.61×10^{-5}	1.65×10^{-4}	4×10^{-6}	1×10^{-5}
	Thinning/Hand Weeding	62	12 hrs	5.01×10^{-5}	1.65×10^{-4}	3×10^{-6}	1×10^{-5}
Grapes	Cane Turning/Girdling	>175	163	1.35×10^{-4}	1.68×10^{-4}	8×10^{-6}	1×10^{-5}
	Hand Harvest	165	120	7.14×10^{-5}	1.65×10^{-4}	4×10^{-6}	1×10^{-5}
	Hand Line Irrigation	75	13	4.98×10^{-5}	1.64×10^{-4}	3×10^{-6}	1×10^{-5}
	Scouting/Hand Weeding	55	12 hrs	4.64×10^{-5}	1.34×10^{-4}	3×10^{-6}	8×10^{-6}

[A] Restricted entry interval refers to the day that workers can enter treated fields, it is the day when metiram residues are less than the target residue limit as presented in Appendix II – Table 5 or the day that the calculated MOE for ETU reaches the target MOE as presented in Appendix II – Table 5.

[B] LADD (Lifetime Average Daily Dose, mg/kg bw/day) calculated based on the metiram or ETU REI day using the following formula:

$$\text{LADD: } \frac{\text{Absorbed Daily Dose ETU (mg/kg bw/day)} \times \text{Treatment Frequency (30 days/yrs)} \times \text{Working Duration (40 yrs/lifetime)}}{\text{365 days/yrs} \times \text{Life Expectancy (75 yrs)}}$$

[C] Cancer Risk, calculated using the following formula: Cancer Risk = LADD (mg/kg bw/day) × q_1^* (0.0601 mg/kg bw/day)$^{-1}$

Appendix VI Dietary Exposure and Risk Estimates for Metiram

Table 1 Acute and Chronic Dietary Exposure and Risk Estimates for Metiram

Population Groups	Acute risk		Chronic risk	
	Exposure (mg/kg bw/day)	% ARfD	Exposure (mg/kg bw/day)	% ADI
General Population	N/A	N/A	0.000447	18
All Infants (<1 year old)	N/A	N/A	0.001320	53
Children 1-2 years old	N/A	N/A	0.003188	128
Children 3-5 years old	N/A	N/A	0.001731	69
Children 6-12 years old	N/A	N/A	0.000648	26
Youth 13-19 years old	N/A	N/A	0.000268	11
Adults 20-49 years old	N/A	N/A	0.000205	8
Adults 50+ years old	N/A	N/A	0.000236	10
Females 13-49 years old	0.070503	88	0.000221	9

ADI Acceptable daily intake = 0.0025 mg/kg bw/day

ARfD Acute reference dose = 0.08 mg/kg bw/day for females 13-49 years of age

Note: The metiram risk estimates are from food alone, as metiram is not expected to occur in drinking water

Table 2 Acute and Chronic Dietary Exposure and Risk Estimates for ETU

	Acute assessment						Chronic assessment					
Population Groups	Food exposure		Food + water exposure		Water exposure		Food exposure		Food + water exposure		Water exposure	
	Exposure (mg/kg bw/day)	% ARfD	Exposure (mg/kg bw/day)	% ARfD	Exposure (mg/kg bw/day)	% ARfD	Exposure (mg/kg bw/day)	% ADI	Exposure (mg/kg bw/day)	% ADI	Exposure (mg/kg bw/day)	% ADI
General Population	N/A	N/A	N/A	N/A	N/A	N/A	0.000142	24	0.000203	34	0.000061	10
All Infants (<1 year old)	N/A	N/A	N/A	N/A	N/A	N/A	0.000370	62	0.000571	95	0.000200	33
Children 1-2 years old	N/A	N/A	N/A	N/A	N/A	N/A	0.000549	92	0.000640	107	0.000091	15
Children 3-5 years old	N/A	N/A	N/A	N/A	N/A	N/A	0.000345	58	0.000430	72	0.000085	14
Children 6-12 years old	N/A	N/A	N/A	N/A	N/A	N/A	0.000156	26	0.000214	36	0.000059	10
Youth 13-19 years old	N/A	N/A	N/A	N/A	N/A	N/A	0.000080	13	0.000124	21	0.000044	7
Adults 20-49 years old	N/A	N/A	N/A	N/A	N/A	N/A	0.000109	18	0.000166	28	0.000057	10
Adults 50+ years old	N/A	N/A	N/A	N/A	N/A	N/A	0.000119	20	0.000179	30	0.000060	10

	Acute assessment						Chronic assessment					
Population Groups	**Food exposure**		**Food + water exposure**		**Water exposure**		**Food exposure**		**Food + water exposure**		**Water exposure**	
	Exposure (mg/kg bw/day)	**% ARfD**	**Exposure (mg/kg bw/day)**	**% ARfD**	**Exposure (mg/kg bw/day)**	**% ARfD**	**Exposure (mg/kg bw/day)**	**% ADI**	**Exposure (mg/kg bw/day)**	**% ADI**	**Exposure (mg/kg bw/day)**	**% ADI**
Females 13-49 years old	0.002341	47	0.002820	56	0.000779	16	0.000112	19	0.000169	28	0.000057	10

ARfD: Acute reference dose =0.005 mg/kg bw/day
ADI: Acceptable daily intake =0.0006 mg/kg bw/day

Table 3 Cancer Dietary Exposure and Risk Estimates for ETU

Population Group	**Food exposure**		**Food and water exposure**		**Water exposure**	
	Exposure (mg/kg bw/day)	**Lifetime risk**	**Exposure (mg/kg bw/day)**	**Lifetime risk**	**Exposure (mg/kg bw/day)**	**Lifetime risk**
General Population	0.000142	9×10^{-6}	0.000203	12×10^{-6}	0.000061	4×10^{-6}

Cancer risk = Exposure (mg/kg bw/day) × q1* $(0.0601 \text{ mg/kg bw/day})^{-1}$

Appendix VII Food Residue Chemistry Summary

1.1 Metabolism

The PMRA concluded that the nature of residues for metiram and ethylenebis(dithiocarbamate) (EBDC) in plants and livestock is adequately understood. In all studies, EBDCs are susceptible to decomposition even under normal storage conditions when exposed to oxygen and moisture. The degradations of the EBDCs in water, soil, plants and animals follow common pathways. Disassociation of the metal complex and oxidation reactions lead to the formation of carbon disulfide, ethylenethiuram disulfide (ETD), ethylenethiuram monosulfide (ETM) and isothiocyanate as major products. The structure of ethylenethiuram monosulfide in the literature was ambiguous and it was subsequently confirmed as 5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazole-3-thione (DIDT). Further degradation yielded ethylene thiourea (ETU), ethylene urea (EU) and 2 imidazoline as terminal products.

The formation and degradation of ETU have been extensively investigated since toxicological studies had confirmed the carcinogenic/teratogenic potential of ETU. ETU is a decomposition product of the various EBDC formulated products and is also a hydrolytic degradation product. It can be generated directly from the parent compound and/or from DIDT via a thiocarbamic acid intermediate.

1.1.1 Plant metabolism

The nature of metiram residues in the registered crops is adequately understood based on the submitted metiram metabolism studies in apples and potatoes. These studies indicate that the majority of the total radioactive residues (TRR) are present in natural products. The residues of concern are the parent metiram and ETU.

Potato

Three potato metabolism studies realized with radiolabelled ^{14}C metiram were submitted for review. The results of the studies are consistent and show an extensive transformation of metiram in natural occurring products such as creatinine, allantoin, creatine, glycine and hydantoin, or it was incorporated in natural products such as starch, aminoacids, cellulose and hemicellulose. In one of the studies performed at higher than GAP application rate, ETU, EU, DIDT/ETT and N-acetyl-EDA were detected in very small amounts and it was concluded that they were minor metabolites. They are considered to be dynamic intermediates that lead to other metabolites. Low levels of ETU were detected in pulp or in peel.

Apples

Two apple metabolism studies realized with radiolabelled ^{14}C metiram were submitted for review. The results of the two studies are consistent and show a low transformation of metiram in metabolic products such as creatinine, allantoin, creatine, glycine, hydantoin, ETU, EU, EDA, EDTC, EBIS, DIDT/ETT, N-formylglycine and N-acetyl-EDA with trace or non-detectable residue level. The major component found was the parent metiram. The highest radiolabelled concentration of ETU in the fruit was of 0.054 mg/kg in terms of metiram equivalent and 0.21 mg/kg in the peel.

1.1.2 Animal metabolism

The nature of metiram residue in livestock is adequately understood based on the submitted goat and poultry metabolism studies

The metabolism of metiram in animals generates a large number of metabolites found in all tissues. EU and Jaffe's Base were found to be the major metabolites. ETU was not the major metabolite detected in the analysed samples, but was a dynamic intermediate leading to other metabolites. The parent compound was metabolised to EDA and hydantoin and then converted to glycine, which entered the metabolic pools and was incorporated further in natural products like lipids and proteins. Based on the submitted data the residue of concern are the parent metiram and ETU.

Ruminant

Two metabolism studies were each performed on two lactating goats which were dosed orally for 5 successive days by capsule with radiolabelled metiram with [*ethylenediamine*-^{14}C]metiram or with 1.6 g [*thiocarbamoyl*-^{14}C]metiram, equivalent to 50 or 1000 ppm metiram in the feed. Milk was collected throughout, and the animals were slaughtered 5-8 hours after the final dose for tissue and organ collection.

The peak level in milk was reached on the 4th day. The highest levels of metabolites were found in the thyroid, liver and kidneys. ETU and EU attained important level in milk and tissue samples but were not the major metabolites. A major unidentified metabolite found in extracts of milk, kidneys, liver and muscle, represented 40% and 66% of the two ^{14}C in day-4 milk, corresponding to 14 and 15 mg/kg. The estimated levels in kidneys were 48 and 39 mg/kg, in liver 25 and 22 mg/kg, and in muscle 7 and 4 mg/kg.

Most of the ^{14}C (with the highest level of 75% of the dose, on day 4) was excreted in the faeces. Excretion in the urine was also high; on the basis of the level of ^{14}C, in the day 5 evening sample, it was estimated that 54% of the dose was excreted in the urine. The total ^{14}C in the liver, kidneys, muscle and fat accounted for 1.5%, 0.17%, 0.03% and 0.02% of the administered dose respectively. The levels of ^{14}C in the milk rapidly reached a plateau within 1-2 days, and the total ^{14}C excreted in the milk (calculated from the level in the day 4 evening milk) attained approximately 0.77% of the dose.

A number of the metabolites were identified in the tissues and milk. The ^{14}C TRR levels expressed as metiram were milk 0.61, liver 6.27, kidneys 3.71, muscle 0.38 and fat 0.25 mg/kg. Jaffe's base was a major metabolite in the milk (29%) and kidneys (40%), while ETU constituted 9.4% of the residue in the fat. Other major metabolites were EU, Allantoin, EDA and glycine, whereas ETU, creatine, creatinine, N-acetyl EDA, N-formylglycine, hydantoin and DIDT (EBIS/ETT) were minor metabolites. A considerable percentage of the ^{14}C in each tissue and in milk had been incorporated into natural products such as lactose, amino acids, proteins, and lipids.

Poultry

A group of 30 laying hens were dosed orally for 7 days by capsule with radiolabelled metiram ([^{14}C]ethylenediamine), equivalent to 50 ppm metiram (90/5131; PMRA#1589620). Eggs were collected throughout, and birds were slaughtered 8 hours after the final dose for tissue and organ collection. The levels of metiram and ETU in the tissues and eggs reached the highest level in liver and kidneys at 0.17 ppm metiram and 0.1 ppm ETU. The major metabolite in all samples was EU. ETU was consistently present at 1.8-4.9% of the total ^{14}C. Lipids and proteins contained ^{14}C – up to 20.3 and 41.6% of TRR, respectively, showing that some of the metiram had been converted to natural products.

A second feeding/metabolism study was made on two groups of 10 laying hens which were dosed orally for 5 days by syringe with radiolabelled metiram (^{14}C thiocarbamoyl and ^{14}C ethylenediamine, respectively), equivalent to 1025 and 986 ppm metiram. Eggs were collected throughout, and birds were slaughtered 5 hours after the final dose for tissue and organ collection. Results show that 80-85 % of the TRR was found in the excreta. Detectable TRR were found in liver, skin, muscles and eggs.

Based on the use pattern of metiram on the registered crops, it is not expected to find any residues in the poultry commodities via the consumption of feed commodities derived from metiram treated crops, as they are not fed to poultry.

1.1.3 Residue Definition

The qualitative nature of metiram residues in plant and animal is well understood based on reviews of acceptable plant and animal metabolism studies. As the cancer potency factor for all the EBDCs is derived from ETU, the PMRA has concluded that both the metiram and its ETU metabolite must be included in the risk assessment. As it is known that the analytical methods convert most of the metabolites of the EBDCs to CS_2 and that the amount of ETU in raw and processed commodities can not be considered as a reliable indicator for metiram, the PMRA has concluded that for enforcement purpose, the MRLs should be expressed in CS_2.

The current residue definition for all EBDCs in all commodities is expressed as manganese and zinc ethylenebis(dithiocarbamate) (polymeric), also known as zineb. Expressing EBDC residues as such a surrogate chemical is no longer consistent with international practice. The United States, Codex and the European Union establish their MRLs on total dithiocarbamates, determined as CS_2 and expressed as mg CS_2/kg.

1.2 Analytical Methods

1.2.1 Methods for Residue Analysis in Plants

Method 135 (Keppel Method) was proposed for the analysis of metiram or other dithiocarbamates in plant samples (salad, cucumbers, tomatoes, apples, grapes, currants, cereals, cherries, plums, hops, Brussels sprouts, beans, celery). The method is based on generation of CS_2 from metiram heated and distilled from a hydrochloric acid solution and absorbed in a KOH-methanol solution forming a xanthogenate which is analysed by UV spectroscopy. In case of interferences the xanthogenate is derived to form N,N-di-n-propyl-dithiocarbamic acid methyl ester determined by GC-N-FID or GC-S-FPD. Depending on the analysed plant material the stated LOD is 0.02-0.2 ppm CS_2. Recoveries are mentioned to be in the 70-100% range and UV and GC analysis yield similar results.

A similar method DFG S15[1] determines and calculates metiram residue levels in tomato, lemon, wheat (grain) and sunflower (seed) as CS_2. It is a gas chromatography method using flame photometric detection with an LOD of 0.02 ppm metiram as CS_2. The recoveries for a 0.02 ppm metiram as CS_2 fortification in tomato, lemon, wheat (grain) and sunflower (seed) samples were 97%, 93%, 101% and 79%, respectively.

The method MS133.02 determines EBDCs as CS_2 in plant samples by GC/MS with an LOQ of 0.02-0.04 ppm for most plants. The method analyses by GC/MS the CS_2 generated by the treatment of plant samples with a solution of $SnCl_2/HCl/EDTA$.

PMRA has on file the description of method ETU-89AM-001, ETU-89AM-002 and ETU-89AM-003, used to determine the concentration of EBDC in crops and processed crops, meat, and milk respectively. The detection limits were determined to be 0.02 ppm for crops and processed crops, 2 ppb for meat and milk.

The USEPA has also reviewed the ETU-89AM-001 method. The validated limits of quantitation from field trials were 0.05 ppm in banana, cranberry, grape, pear, sugar beet root and top, 0.02 ppm in cottonseed and 0.4 ppm in dry bulb onion.

1.2.2 Methods for Residue Analysis of Food of Animal Origin

Method 135 was amended (Method 135/1) to extend the UV spectroscopic method also to animal samples (eggs, cow urine) and molasses. The LOD in eggs is 0.12 ppm and 1 ppm in urine and molasses. The average recovery is 90.7, 97.7, and 88.4% in eggs, cow urine and molasses, respectively.

An amended method 135/2 was proposed for the determination of poultry eggs, muscle, skin+fat, liver, feed and cow milk, muscle, fat, liver, kidney, urine, molasses, using GC-FPD. The method follows the same procedures in which the samples are distilled with a solution of stannous chloride and hydrochloric acid yielding CS_2 in a stream of nitrogen. The stream is purified from H_2S and other volatile impurities by sequential absorption in a lead acetate solution, a concentrated sulphuric acid solution and a sodium hydroxide solution. The liberated CS_2 is absorbed in two traps and is analysed by GC-FPD. The average recovery level in poultry and cow are 70% and 78%, respectively.

1.2.3 Enforcement Analytical Methodology

The Keppel colorimetric method (designated as Method III in PAM Vol. II; JAOAC, 54:528-532) identical with registrants Method 135 and its subsequent development, may be used for enforcement purpose. The Keppel method, which is not specific to metiram residues but to the EBDC common moiety as it analyses EBDCs as a group by degradation to carbon disulfide, is proposed as the official method for dithiocarbamates including metiram.

1.2.4 Inter-Laboratory Validation (ILV)

An independent laboratory validation study of the analytical method DFG S15 [1] was presented for the metiram determination, in tomato, lemon, wheat (grain), sunflower (seed) by UV spectrophotometry. The LOD was established at 0.02 ppm metiram as CS_2. The average recoveries in tomato, lemon, wheat (grain), sunflower (seed) were 97, 93, 101 and 79%, respectively.

The study validates the amended method 135/2 which determines and calculates metiram residue levels in animal matrices as CS_2. It is a gas chromatography method using flame photometric detection with an LOD of 0.02 mg/kg. The recoveries for a 0.02 mg/kg fortification in liver and muscle samples were 100% and 112%, respectively, whereas for a 0.2 mg/kg fortification the recoveries were 84% and 80%, respectively.

A gas-liquid chromatographic procedure for the determination of traces of ethylene thiourea in fresh vegetables, fruits, milk and cooked foods has been successfully collaboratively studied and validated (Onley, 1977b). The method is designed to determine ETU without interference from EBDC fungicides by conversion of ETU to S-butyl derivative. The results of the method showed average recoveries from crops and milk at a fortification level of 0.06; 0.12 and 0.30 ppm ranging from 85 to 97%

The Table 2 summarizes the submitted analytical methods indicating their acceptability and if they were validated.

Table 2 Summary of Analytical Methods

Method	Analyte	Plants				Animals			
		Matrix	Metab.	Accept.	ILV	Matrix	Metab.	Accept.	ILV
RAR 570	EDA	Potato	EBDC	Y	N	Milk	EBDC	Y	N
-	ETU	NS	ETU	Y	Y	NS	ETU	Y	Y
RUA 1/91-I	ETU	NS	ETU	N	N	NS	ETU	N	N
RUA 1/91-I	CS_2	NS	EBDC	N	N	NS	EBDC	N	N
Onley	ETU	Fresh vegetables, fruits, cooked foods	ETU	Y	Y	Milk, cooked foods	ETU	Y	Y
135	CS_2	Salad, cucumbers, tomatoes, apples, grapes, currants, cereals, cherries, plums, hops, Brussels sprouts, beans, celery	EBDC	Y	Y				
135/1	CS_2	Molasses	EBDC	Y	N	Eggs, cow urine	EBDC	Y	N
135/2	CS_2	Feed, Molasses	EBDC	Y	Y	Poultry, eggs, diary, milk	EBDC	Y	Y

Method	Analyte	Plants				Animals			
		Matrix	Metab.	Accept.	ILV	Matrix	Metab.	Accept.	ILV
DFG S15	CS_2	Tomato, lemon, wheat (grain), sunflower (seed)	EBDC	Y	Y				
MS133.02	CS_2	Most plants	EBDC	N	N				
ETU 89AM 001	CS_2	Crops and processed commodities	EBDC	Y	Y				
ETU 89AM 002	CS_2					Meat	EBDC	Y	Y
ETU 89AM 003	CS_2					Milk	EBDC	Y	Y

Note: NS – not stated; Accept – acceptable; Y – yes; N – no, ILV – independent laboratory validation

1.2.5 Multi-Residue Analytical Method (MRM)

The USEPA stated that the metiram and ETU are not recovered using any of the FDA's Multiresidue Protocols. The recovery of metiram using FDA Multiresidue Protocol A-E and 232.3 was not attained as well. The FDA Pestdata database (10/99) indicates that there is a small recovery (<50%) of ETU using Method 302 (Luke method; Protocol D) but ETU is not recovered using Method 303 (Mills, Onley, and Gaither method; Protocol E) and 304 (Mills method for fatty food).

Similar results were obtained in the study BASF 88/5539 and BASF 88/5540 where metiram was not detected in the multiresidue protocols tested and ETU was detected with low recoveries.

1.3 Food Residues

1.3.1 Storage Stability

1.3.1.1 Freezer Storage Stability in Plants

Storage stability studies for metiram and ETU were submitted for the following raw agricultural commodities (RAC): apples, sugar beets, potatoes and tomatoes and on the processed commodities of apples and potatoes. Metiram has proved to be stable for up to three months on all fortified RAC tested. Weathered metiram residues were also stable for three months on frozen whole apples.

ETU was stable in fortified tomatoes but was instable and was not recovered from chopped apples, potatoes and sugar beets. Analysis of weathered ETU residues on whole frozen apples showed the stability over time. It was shown that the ETU instability was form specific. It is estimated that the instability in chopped RAC is due to the catalytic nature of the cut surfaces and appears to be a function of the degree of cell rupture and release of enzymes, natural chemicals, or other cellular materials capable of facilitating EBDC and/or ETU degradation and it is not indicative of the ETU stability in whole RAC samples.

From the available data it was concluded, that the conversion of metiram to ETU during frozen storage was limited, with the highest value of 7% or 0.05ppm in potatoes.

Similarly, metiram is stable in potato processed commodities but ETU was stable only in potato chips. Conversion of metiram to ETU in potato processed commodities is not significant.

The summary of the storage stability is presented in Table 3. Metiram presented a longer storage stability than ETU, which for most analyzed commodities was not stable for more than 2 weeks.

Table 3 Summary of Storage Stability for Metiram and ETU

Commodity	Stability (months)	
	Metiram	ETU
Apples	12	0.5
- Sauce	12	3
- Juice	12	12
- Baby food	12	12
- Wet pomace	3	0.5
- Dry pomace	3	3
Tomatoes	12	12
- Processed commodities	3	3
Potato	12	<0.5
- Dry/Wet peel	3	<0.5
- Chips	12	<0.5
- Granules	6	<0.5
Sugar beet (diced)	12	-
- Roots	3	-
- Crystalline sugar	3	-
- Dehydrated pulp	3	-
- Molasses	3	6
Grapes	18	-
Peanut nutmeat	6	1
- Hulls	6	0.5
Pecan	3	1
Banana	1	1
- Pulp	1	1

1.3.1.2 Freezer Storage Stability in Animals

The storage stability of metiram and ETU in animal commodities (beef, poultry, eggs and milk) was shown that both compounds were found stable over a period of 26 weeks of frozen storage of samples fortified with 2.0 ppm metiram and 0.5 ppm ETU. There is no significant conversion of metiram to ETU, the highest value of 0.04 ppm was attained for whole eggs after a 26 week storage. As the consumption of animal commodities implies a limited or no storage period, an insignificant conversion of metiram to ETU is expected in those commodities.

1.3.1.3 Storage Stability of Working Solutions in Analytical Methodology

There are no storage stability studies for working solutions submitted by the registrant. The registrant is required to submit such storage stability studies for any expansion of use of metiram.

1.3.2 Crop Residues

Crop residue data were available from registrant field trial studies, the EBDC/ETU National Food Survey which is an industry sponsored market basket survey (MBS) conducted in the United States (Atochem NA Inc, BASF, E.I. du Pont de Nemours, Rohm and Haas), the USEPA RED and data from the Metiram Task Force.

EBDC/ETU National Food Survey

In 1989 the industry EBDC/ETU task force conducted a national scale survey for actual residues of both EBDCs and ETU which may exist in fresh and processed foods as obtained from marketplace shelves in the contiguous United States. This MBS survey was conducted over the course of a year, and included nearly 6000 samples which were analyzed both for ETU and EBDCs. The analyzed commodities include: almonds, infant apple juice, apple juice, apple sauce, raw grapes, raisins, canned green beans, frozen green beans, infant green beans, raw green beans, dried kidney beans, canned kidney beans, raw broccoli, frozen broccoli, celery, raw corn, canned corn, frozen corn, cucumbers, lettuce, beef top round, milk, onion, raw potatoes, frozen potatoes, raw tomato, tomato juice, tomato ketchup, tomato paste and tomato puree.

The results from the year long study provided information on residue levels of EBDCs and ETU in the food supply. Specifically, for all four quarters of the survey, 81% of the 5888 food samples analyzed for EBDCs did not contain detectable residues, and 82% of the 5890 samples analyzed for ETU did not contain measureable residues and the residues of EBDC and ETU were generally lower than the MRLs or field trials.

In conjunction with the EBDC/ETU National Food Survey, separate surveys were conducted for bananas, grape juice, wine, and apples. Bananas known to have been treated with EBDCs during growth were obtained from growers or packers and analyzed for residues shortly after harvest. Processed grape commodities (wine and fresh juice) were obtained from areas of the United States where EBDC usage on grapes is extensive in an attempt to assess the upper range of residues which might be encountered for grape products.

Since the survey is over 20 years old and the registered EBDC use pattern has changed since then in both Canada and the United States, there is uncertainty in the use of those data for risk assessment purposes. Also there are differences in the use pattern between the United States and Canada. Therefore the MBS data was only be used to characterize residues on imported commodities from the United States to Canada. A summary of the residue data from the MBS are included in Table 4, below.

Residue data from field trials and other sources

Review of the submitted residue field trial studies has identified several data deficiencies. The available data do not conform to the regulatory standard for asparagus, carrot, celery, grapes, sugar beets and tomatoes. Supervised residue field trials measuring both metiram and ETU performed in Canadian regions according to Canadian GAP are not available. Such data are considered to be a requirement for considered registration for any food use pesticide.

A summary of the available residue data in the registered commodities (Canada and the United States) determined as highest average field trial (HAFT) and supervised trial mean/median residue (STMR), is presented below. Field trial data from climatic zones outside of Canada and at rates outside of the Canadian GAP are included where this represents the best available data. The residue data are reported as zineb equivalents or as CS_2. Residue data from sources other than supervised field trials, such as the MBS, are also presented. Where appropriated, the average and maximum residues were calculated and presented in HAFT and STMR columns.

Table 4 Metiram and ETU residues in plant commodities

Apple						
Residues			Metiram (ppm)		ETU (ppm)	
			HAFT	STMR	HAFT	STMR
Expressed as: (z – zineb) (c – CS_2)	Field trials	Apples	1.05 z 0.59 c	0.23 z 0.13 c	0.013	0.004
		Apple sauce	0.41 z 0.23 c	0.34 z 0.19 c	0.06	0.05
		Baby food	0.12 z 0.07 c	0.12 z 0.07 c	0.08	0.08
		Apple juice	0.45 z 0.25 c	0.15 z 0.08 c	0.04	0.012
		Cooked juice	0.1 z 0.06 c	0.1 z 0.06 c	0.08	0.08
		Dry pomace	0.96 z 0.54 c	0.69 z 0.38 c	0.014	0.008
		Wet pomace	0.30 z 0.17 c	0.20 z 0.11 c	0.01	0.005
	Task force residues	Apples	0.77 z 0.43 c	0.59 z 0.33 c	0.039	0.031
	Market Basket Survey (MBS)	Apples	1.7 z	0.14 z	0.123	0.009
		Apple sauce	0.104z	0.037z	0.032	0.007
		Apple juice	0.093z	0.012z	0.04	0.005
		Infant juice	0.233z	0.013z	0.015	0.005

Asparagus						
Residues			Metiram (ppm)		ETU (ppm)	
(z – zineb) (c – CS_2)			HAFT	STMR	HAFT	STMR
	Field trials	Asparagus	-	-	-	-
	Market Basket Survey (MBS)	Asparagus	-	-	-	-
Carrot						
Residues			Metiram (ppm)		ETU (ppm)	
(z – zineb) (c – CS_2)			HAFT	STMR	HAFT	STMR
	Field trials	Asparagus	-	-	-	-
	Market Basket Survey (MBS)	Asparagus	-	-	-	-
Celery						
Residues			Metiram (ppm)		ETU (ppm)	
(z – zineb) (c – CS_2)			HAFT	STMR	HAFT	STMR
	Field trials	Celery	-	-	-	-
	Market Basket Survey (MBS)	Celery	0.37	0.04	0.024	0.006
		Weighted mean	-	0.03	-	0.002
Grape						
Residues			Metiram (ppm)		ETU (ppm)	
(z – zineb) (c – CS_2)			HAFT	STMR	HAFT	STMR
	Field trials (Europe only) Note: HAFT residue values were chosen from the field trials that were done at rates, number of applications and preharvest interval nearest to Canadian GAP	Grapes	4.45 z 2.37 c	2.23 z 1.22 c	0.04	0.033
		Raisins	19.3 z 10.8 c	9.58 z 5.36 c	0.133	0.064
		Wine	0.31 z 0.17 c	0.12 z 0.06 c	1.4	0.44
		Vine leaves	11.2 z 6.26 c	6.84 z 3.83 c	0.064	0.055
		Pomace	11.3 z 6.33 c	6.14 z 3.43 c	0.166	0.112
	Task force residues	Grapes	-	-	-	-
	Market Basket Survey (MBS)	Grapes	1.98 z	0.07 z	0.074	0.005
		Raisins	0.99 z	0.06z	0.066	0.004
		Grape juice	0.24z	0.024z	0.024	0.005
Potato						
Residues			Metiram (ppm)		ETU (ppm)	
(z – zineb) (c – CS_2)			HAFT	STMR	HAFT	STMR
	Field trials	Tubers	0.9 z 0.51 c	0.26 z 0.14 c	0.07	0.035
		Pulp	0.97 z 0.54 c	0.39 z 0.22 c	0.01	0.005
		Peel	0.69 z 0.38 c	0.29 z 0.16 c	0.03	0.03
		Chips	0.01z 0.06 c	0.005z 0.03 c	0.01	0.005
		Dehydrated granules	0.01z 0.06 c	0.005z 0.03 c	0.01	0.005
		Flakes	0.01z 0.06 c	0.005z 0.03 c	0.01	0.005
	Task force residues	Tubers	0.15 z 0.08 c	0.11 z 0.06 c	0.04	0.018
	Market Basket Survey (MBS)	Raw potato	0.21 z	0.003z	0.107	0.003
		Frozen potato	0.01 z	0.003z	0.014	0.005
		Raw potato	-	0.002z	-	0.002

		(weighted mean)				
		Frozen potato (weighted mean)	-	0.001z	-	0.004
Sugar beet						
Residues			Metiram (ppm)		ETU (ppm)	
(z – zineb) (c – CS_2)			HAFT	STMR	HAFT	STMR
	Field trials	Sugar beets	1.94 z 1.09 c	0.44 z 0.25 c	0.502	0.133
		Dried pulp	1.04 z 0.58 c	0.99 z 0.56 c	0.22	0.14
		Molasses	0.09 z 0.05 c	0.07 z 0.04 c	2.3	1.7
		White sugar	0.05 z 0.03 c	0.05 z 0.03 c	0.01	0.005
	Task force residues	Sugar beets	-	-	-	-
	Market Basket Survey (MBS)	Sugar beets	-	-	-	-
Tomato						
Residues			Metiram (ppm)		ETU (ppm)	
(z – zineb) (c – CS_2)			HAFT	STMR	HAFT	STMR
	Field trials	Tomatoes	3.13 z 1.75 c	0.34 z 0.19 c	0.037	0.013
		Canned tomatoes	0.07 z 0.04 c	0.06 z 0.03 c	0.034	0.026
		Tomato juice	0.46 z 0.26 c	0.09 z 0.05 c	0.11	0.033
		Ketchup	0.11 z 0.06 c	0.04 z 0.02 c	0.24	0.037
		Pulp	0.33 z 0.18 c	0.05 z 0.03 c	0.02	0.014
		Peels	8.85 z 4.95 c	1.97 z 1.10 c	0.074	0.025
		Puree	0.73 z 0.41 c	0.29 z 0.16 c	0.388	0.125
		Tinned food	0.09 z 0.05 c	0.03 z 0.01 c	0.02	0.01
		Peeled tomatoes	0.07 z 0.04 c	0.06 z 0.03 c	0.02	0.011
	Market Basket Survey (MBS)	Tomatoes	0.49 z	0.03 z	0.034	0.003
		Juice	0.03 z	0.006z	0.021	0.004
		Juice (w. mean)	-	0.002z	-	0.002
		Ketchup	0.06 z	0.006z	0.017	0.004
		Ketchup (w. mean)	-	0.002z	-	0.002
		Paste	0.32 z	0.013z	0.04	0.007
		Paste (w. mean)	-	0.063z	-	0.006
		Puree	0.02 z	0.009z	0.031	0.008
		Puree (w. mean)	-	0.002z	-	0.003

1.3.3 Livestock Residues

Three acceptable livestock feeding studies were reviewed, one performed on lactating dairy cows and two on poultry. The studies were performed at multiple rates: at MTDB estimated rates and exaggerated rates

Poultry

Poultry feeding studies showed low levels of residues of metiram and ETU in all poultry samples. The birds were treated with metiram at level of 0.3, 1.5, 3.0, and 150 ppm. For the birds treated at the low feeding rates, the residues were below the LOD of 0.05 for metiram and 0.02 for ETU. In eggs the metiram residue level for the highest dose rate do not exceed 0.16 ppm whereas the highest residue level in tissue is not exceeding 0.6 ppm in liver and kidney and 0.5 ppm in fat and muscle for the poultry fed at the highest feeding rate. For ETU the highest level attained in eggs was below 4.2 ppm. In tissues the highest level was obtained in kidneys at 3.3 ppm. Estimates of the MTDB show that potential residues of metiram present in poultry feed would be nil, as the poultry is not fed with any of the registered commodities to be treated with metiram.

Ruminant

A ruminant feeding study was performed on dairy cows fed with exaggerated metiram levels of 40, 200, 400 and 20000 ppm. At the lowest feeding rate (10 × MTDB) the residues would not exceed 0.09 ppm in all tested samples, with the highest level in the subcutaneous fat. The highest residue level 10 ppm in liver samples was obtained at the highest feeding rate (~5000 × MTDB). No detectable metiram residues are expected to be found in dairy cow samples or milk from animals fed with metiram treated crops at Canadian GAP rate.

In conclusion, the results from the animal feeding studies show that no detectable residues of metiram or ETU are expected to be found in any animal samples, eggs or milk taken from animals fed with metiram treated crops at GAP rate.

1.3.4 Confined and Field Crop Rotation

A confined rotational crop measured the degradation of a radiolabelled metiram soil application in soil and three rotational crops (wheat, kale and beets) after application. Metiram was applied at a rate of 8.7 ppm (metiram in soil) and subsequent planting of the crops was done at 29,143 and 379 days after application. Sampling of the three crops was made at about 50, 80 and 130 days after each planting. The distribution of the radiolabelled ^{14}C in crops showed the highest level in wheat straw, whereas the kale contained the lowest level throughout the study. The inconsistent results throughout the trial as well the incomplete identification of the nature and amount of metiram residue uptake in rotational crops make the submitted data unacceptable. Confirmatory rotational crop data is required to the registrant for any expansion of use.

1.3.5 Processed Food/Feed Data

The usage or transformation process, employed for the various crops for transforming them in valuable commodities, has an important impact on the residue level of a particular pesticide or metabolite in the respective commodities. Studies for the fate of the residues following consumer practices or industrial processing were submitted and reviewed by PMRA.

During the re-evaluation process and review of the scientific literature, it was determined that generally, metiram residues remain on the surface of the raw agricultural commodity. Some conversion of metiram to ETU may occur, but most of the residues on the RAC are the parent. If some conversion to ETU has occurred, the ETU residues are able to transfer across the surface of the edible commodity and are able to spread throughout the plant. Therefore, washing, trimming and peeling the raw commodity causes considerable reduction of surface metiram residues, but not for "systemic" ETU residues. However, peeling has been found to reduce ETU residues on thick-skinned commodities such as bananas, mangoes and melons. Heating commodities reduces ETU slightly and causes some conversion of metiram residues to ETU. Processes involving cooking of commodities result in a conversion of the EBDC to ETU.

As some commodities may be subjected to multiple steps during processing, an overall factor combines the multiple processing steps (individual factors are multiplied) to yield a single factor. PMRA has reviewed several processing studies submitted by the EBDC/ETU Task Force to support the registration of metiram. These studies clearly show discrepancies between the processing factor values. The PMRA also concluded that the majority of the ETU residues formed after processing may be avoided by a sound washing of the EBDC residues present on the RAC.

To conduct the Dietary Exposure Assessment, the PMRA has followed recommendations adopted in the OECD guideline for the testing of chemicals describing the magnitude of the pesticide residues in processed commodities. The processing studies should simulate industrial or domestic practices as closely as possible. RACs used in processing studies should contain field-treated quantifiable residues, at sufficient levels that concentration/reduction factors for the various consumed products can be determined. However, results from the PMRA review showed that some studies did not comply with such recommendation.

1.3.5.1 Consumer Practices Studies

Consumer practices include all processes performed in the household for the food preparation like washing, brushing, peeling etc. Data was submitted by the EBDC/ETU task force to characterize the reduction in residues which may occur during those processes applied on treated food commodities. However there was insufficient information regarding to the extent of those practices in the Canadian households, to use them in a quantitative fashion, therefore these factors were not used.

1.3.5.2 Processing Factors

Processing factors were obtained from field trials, market basket survey data, task force residue summaries and the USEPA RED. These factors represent the transformation of the residues in industrially prepared food commodities from treated crops. A summary of the processing factors derived from field trial data is provided in the Table 5. High, average and low values were presented for the respective commodities as for some commodities multiple data were available.

Table 5 Metiram and ETU Processing Factors derived from field trials

		Metiram			ETU		
Crop	**Commodity/Process**	**Lowest value**	**Mean value**	**Highest value**	**Lowest value**	**Mean value**	**Highest value**
Apples	Sauce	0.09	0.22	0.32	1.22	1.24	>3.00
	Baby food	0.05	0.05	0.05	1.15	1.15	1.15
	Cooked juice	<0.05	<0.05	<0.05	1.22	1.22	1.22
	Dry pomace	3.17	7.39	12.95	>2.84	8.54	15.48
	Juice	<0.05	0.20	0.39	0.57	1.11	>1.50
	Wet pomace	0.75	2.39	4.64	2.29	2.74	3.19
Grape	Must	0.04	0.32	0.90	0.22	3.92	13.90
	Cold must	0.01	0.17	0.48	1.00	2.00	>3.50
	Heated must	0.01	0.19	0.56	>2.50	>2.50	>2.50
	Must from heated mash	0.56	0.56	0.56	>1.50	>1.50	>1.50
	Must pasteurized	1.40	1.55	1.70	8.90	14.10	19.30
	Must unpasteurized	1.80	1.85	1.90	0.46	0.67	0.88
	Must fermented	0.01	0.13	0.25	1.00	1.00	>1.00
	Pomace	0.60	1.64	3.74	0.30	2.26	7.27
	Raisin	0.71	3.33	4.96	0.80	1.67	3.33
	Wine	0.01	0.024	0.05	0.61	5.37	13.83
	Wine mature pasteurized	0.02	0.025	0.03	9.50	14.55	19.60
	Wine mature unpasteurized	0.01	0.02	0.03	9.60	12.50	15.40
	Wine maturing cold must	<0.01	0.015	0.02	>3.50	>3.50	>3.50
	Wine maturing fermented must	<0.01	<0.01	<0.01	>2.00	>2.00	>2.00
	Wine maturing heated must	0.02	0.02	0.02	>3.50	>3.50	>3.50
	Wine young	0.01	0.017	0.03	1.30	5.77	10.50
	Wine young, pasteurized	0.02	0.045	0.07	3.80	6.20	8.60
Potato	Chips	-	-	-	0.06	0.06	0.06
	Dehydrated granules	-	-	-	0.06	0.06	0.06
	Flakes	-	-	-	-	-	-
	Pulp	1.07	1.73	2.44	0.20	0.20	0.20
Sugar Beets	Dry pulp	7.54	11.17	14.80	2.25	2.93	3.62
	Molasses	0.19	0.43	0.67	40.64	43.95	47.25
	White sugar	-	-	-	-	-	-
Tomato	Canned tomatoes	0.02	0.04	0.07	0.92	1.34	2.50
	Dry pomace	0.22	0.22	0.22	1.00	1.00	1.00
	Juice	0.02	0.88	2.80	>1.50	2.92	4.10
	Ketchup	0.055	0.56	0.75	>1.00	6.65	>12.00
	Pulp	<0.20	1.5	5.50	>1.00	>1.00	>1.00
	Puree	0.067	0.32	0.72	8.31	11.46	15.40
	Canned food	<0.02	<0.02	<0.02	<0.10	0.49	<0.75
	Wet pomace	0.12	0.12	0.12	1.43	1.43	1.43

Table 6 presents a summary of additional commercial processing factors derived from studies which examined the change in residue level following the indicated treatments. These are not considered as guideline studies since the treatment history for the RAC is unknown. The average values used in the risk assessment were presented in bolded italic characters.

Table 6 Metiram and ETU Commercial Processing Factors

Apple						
Processing factors			Metiram high	Metiram average	ETU high	ETU average
	Commercial processing	Washing (residue trials)	0.81	***0.62***	0.05	0.05
		Consumer washing	0.48	0.48	-	-
		Drying	0.27	***0.27***		
		Consumer washing+waxing	0.29	0.29	-	-
		Boiling	0.06	***0.06***	0.87	***0.87***
		Baking	0.06	***0.06***	0.87	***0.87***
Asparagus						
Processing factors						
	Commercial processing	Washing	-	***0.3***	-	-
		Cooking	-	***0.03***		***0.87***
		Washing+cooking	-	***0.009***	-	***0.87***
Carrot						
Processing factors						
	Commercial processing	Washing	-	0.033	-	-
		Washing+peeling	-	***0.14***	-	-
		Cooking	-	***0.03***	-	***0.87***
		Juice - uncooked	-	***0.5***	-	-
		Juice - cooked	-	***0.03***	-	***0.87***
Celery						
Processing factors						
	Commercial processing	Washing+trim	-	***0.045***	-	-
		Cooking	-	***0.03***	-	***0.87***
		Juice - uncooked	-	***0.5***	-	-
		Juice - cooked	-	***0.03***	-	***0.87***
Grape						
Processing factors						
	Commercial processing	Washing	-	***0.12***	-	-
		Cooking	-	***0.06***	-	***0.87***
		Drying	-	0.27	-	-
		Cooked wine	-	***0.06***	-	0.20
Potato						
Processing factors						
	Commercial processing	Washing	-	***0.37***	-	-
		Cooking	-	***0.03***	-	***0.87***
		Washing+Peeling	-	***0.14***	-	-
		Chips	-	1.5	-	-
		Chips cooked	-	0.045	-	0.87
		Flaking/Flour	-	***3.4***	-	-
		Drying flakes/granules	-	0.102	-	0.87
		Cooking+Freezing	-	0.03	-	0.87

Sugar beet						
Processing factors						
	Commercial processing	Refining/Molasses	-	***0.19***	-	***0.48***
		Cooking	-	0.03	-	0.48
Tomato						
Processing factors						
	Commercial processing	Washing	-	***0.55***	-	-
		Cooking	-	***0.05***	-	***0.87***
		Drying	-	0.27	-	-

Appendix VIII Supplemental Maximum Residue Limit Information - International Situation and Trade Implications

As per Table 1, the MRLs in Canada differ from the corresponding tolerances established in the United States (40 CFR Part 180.217), and differ from Codex MRLs (Codex Pesticides Residues in Food Online Database). Common Canadian MRLs are established for the all ethylenebis(dithiocarbamate) fungicides, while Codex MRLs are set collectively for all dithiocarbamate compounds. Specific U.S. tolerances are set for metiram.

Specific MRLs for animal commodities have not been established but are covered under the general provisions of B.15.002(1) of the *Food and Drug Regulations*. This requires that residues do not exceed 0.1 ppm when no specific MRL has been established.

Residues of ethylene thiourea (ETU) are relevant to the ethylenebis(dithiocarbamate) fungicides. Residues of ETU on good commodities are regulated by B.01.046 and B.01.047 to not exceed 0.05 ppm. Neither American tolerances or Codex MRLs are established for ETU.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For livestock commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

Table 1 Differences Between Canadian MRLs and Other Jurisdictions

Commodity	Canadian MRL (ppm)*	American Tolerances (ppm)**	Codex MRL (ppm)***
Almonds			0.1
Asparagus			0.1
Banana		3	2
Barley			1
Broccoli	7		
Brussels sprouts	7		
Cabbages, Head	7		5
Cauliflower	7		
Carrot			1
Celery	5		
Cherries			0.2
Cranberry			5

Commodity	Canadian MRL (ppm)*	American Tolerances (ppm)**	Codex MRL (ppm)***
Cucumber	4		2
Currants, Black, Red, White			10
Edible offal (mammalian)			0.1
Eggs			0.05
Eggplant	7		
Endives	7		
Garlic			0.5
Grapes	7	5	5
Wine		5	
Hops, Dry			30
Kale			15
Leek			0.5
Lentils	6		
Lettuce,			
Head	7		0.5
Cos or Romaine			10
Mandarins			10
Mango			2
Meat (from mammals other than marine mammals)			0.05
Melons, except watermelon			0.5
Milks			0.05
Mushrooms	7		
Onion			
Dry Bulb	0.5		0.5
Green or Spring	7		10
Oranges, Sweet, Sour (including Orange-like hybrids): several cultivars			2
Papaya			5
Peanut			0.1
Pecan			0.1
Peppers Chili, dried	7		10
Peppers, Sweet (including pimento or pimiento)	7		1
Pome fruits			5
Apples	7	0.5	
Pears	7		
Potato		0.2	0.2
Poultry meat			0.1
Poultry, Edible offal of			0.1
Pumpkins			0.2
Squash, summer			1

Commodity	Canadian MRL (ppm)*	American Tolerances (ppm)**	Codex MRL (ppm)***
Stone fruits			7
Strawberry			5
Sugar beet			0.5
Sweet corn (corn-on-the-cob)			0.1
Tomato	4		2
Watermelon			1
Wheat			1
Winter squash			0.1

* The Canadian residue definition for compliance with MRLs in plant and estimation of the dietary intake in plant and animal commodities: manganese and zinc ethylenebis(dithiocarbamate) (polymeric).

** The American residue definition for compliance with the tolerance levels is to be determined by measuring only those mancozeb/metiram residues convertible to and expressed in terms of the degradate carbon disulfide. American tolerances list accessed 14 June 2011.

*** Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

The Codex residue definition for compliance with MRLs in plant and estimation of dietary intake in plant and animal commodities: total dithiocarbamates, determined as CS_2, evolved during acid digestion and expressed as mg CS_2/kg. The MRLs apply to total residues from the use of any or each of the groups of dithiocarbamates. (1) Group ADI: ferbam & ziram, 0.003 mg/kg bw (1996); thiram, 0.01 mg/kg bw (1992); mancozeb, maneb, metiram & zineb, 0.03

Codex MRL list accessed 14 June 2011

http://www.codexalimentarius.net/pestres/data/pesticides/details.html?id=105

Appendix IX Environmental Assessment

Table 1 Fate and Behaviour in the Environment

Process	Substance	$t_{½}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA #
Terrestrial Environment						
Abiotic Transformation						
Hydrolysis	Metiram parent	33 h pH 5 44 h pH 7 75 h pH 9		SFO	Little information about this study available. Half-life calculated by USEPA	1589671
	Metiram complex	Water	Stable		Takes into consideration dissolution of parent metiram and hydrolysis ETU, EU, hydantoin, carbimid and two unidentified fractions were identified as transformation products. ETU was a major transformation product representing 81.5% of the total applied radioactivity	1589645
		pH 3	Stable			
		pH 5	Stable			
		pH 7	Stable			
		pH 9	Stable			
Hydrolysis – Metiram complex	EU (major @ pH 5, 7, 9)	pH 3 2.71 d	9.0 d	SFO	This portion of the study was designed to determine the kinetics of hydrolysis on the solution products	
		pH 5 – insufficient information to determine, non-detect at study termination				
		pH 7 – 9.7 d	32.2 d	SFO		
		pH 9 – 1.5 d	3080000 d	FOMC		
	ETU (major @ pH 3, 5, 7, 9)	pH 3 – increasing at study termination				
		pH 5 – increasing at study termination				
		pH 7 – increasing at study termination				
		pH 9 – increasing at study termination				
	Carbimid (major @ pH 3, 5, 7 & 9)	pH 3 – 1.02 d	9.3 d	FOMC		
		pH 5 - < 1 d		Observed		
		pH 7 – 1.4 d	4.6 d	SFO		
		pH 9 – 0.98 d	3.3 d	SFO		
	EBIS (major @ pH 3)	pH 3 - < 1 d		Observed		
		pH 5 – not detected				
		pH 7 – not detected				
		pH 9 – not detected				
	UF (2)	pH 3 – increasing at study termination				
		pH 5 – 3.4 d	202 d	FOMC		
		pH 7 stable at study termination				
		pH 9 – insufficient information to determine (< 11 d based on observation)				
	UF (1a)	pH 3 – not detected				
		pH 5 – only detected on day 12				

Process	Substance	$t_{1/2}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA #
		pH 7 – insufficient information to determine				
		pH 9 - not detected				
	Hydantoin	pH 3 – insufficient information to determine				
		pH 5 – only detected on day 20				
		pH 7 – not detected				
		pH 9 – only detected on day 3				
Phototransformation in soil	Parent metiram	Could not be determined – assume stable			Phototransformation is not a significant route of dissipation from soil for parent metiram. A large portion of the applied radioactivity was bound as NER at study termination (53% in irradiated samples and 76.1% in non-irradiated samples). Once converted to metiram complex the estimated half-lives for the transformation products under irradiation can be determined.	1599648
	Carbimid	1.7 d		Observed		
	Hydantion	30 d		Observed		
	EU	35 d		Observed		
	UF (2)	0.97 d		Observed		
	ETU	Constant level				
	UF (1aa), (1ab), (1ac), (1c)	Constant level				
	UF (1b)	Could not be determined				
Phototransformation in water	Parent Metiram	9.34 d (dissolution and phototransformation)	31 d	SFO	High pressure mercury light (relationship between the high pressure Hg lamp and natural sunlight could not be determined). Phototransformation in water is not considered an important route of dissipation for metiram.	1589657 1589650
Biotic Transformation						
Aerobic Loamy sand soil	Parent metiram	0.614 d	5.73 d	FOMC	The dissipation of ***parent metiram*** in soil under aerobic biotransformation is attribuatable to hydrolysis, as such, parent metiram is considered non-persistent.	1589658
	Metiram complex	5.5 d	272 d	DFOP	The ***metiram complex*** was determined to be non-persistent in soil under aerobic conditions. The DT_{50} was determined based on extractable radioactivity. The major transformation products identified were ETU and TDIT. Non-extractable residues increased to a maximum of 48.1% of applied radioactivity and decreased to 32% at study termination.	
Aerobic Loamy sand soil	Parent metiram	0.60 d	7.93 d	FOMC	The dissipation of ***parent metiram*** in soil under aerobic biotransformation is attribuatable to hydrolysis, as such, parent metiram is considered non-persistent. The major transformation products was carbimid.	1589664 & 1589661
	Metiram Complex	1.9 d	7.8 d	DFOP	The ***metiram complex*** was determined to be non-persistent in soil under aerobic conditions. The DT_{50} was determined based on extractable radioactivity. Non-extractable residues were determined	

Process	Substance	$t_{½}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA #
					to increased from 6.9 to 32.5% at study termination.	
Aerobic Loam sand	Parent metiram	0.79 d	2.63 d	SFO	The dissipation of ***parent metiram*** in soil under aerobic biotransformation is attributable to hydrolysis, as such, parent metiram is considered non-persistent.	
	Metiram Complex	3.5 d	26.7 d	DFOP	The ***metiram complex*** was determined to be non-persistent in soil under aerobic conditions. The DT_{50} was determined taking into consideration extractable radioactivity and not the non-extractable residues. Transformation products were not identified. Non-extractable residues were determined to increase from 5.7 to 61.3% at study termination.	
Aerobic loam	Parent metiram	9.1 d	166 d	FOMC	The dissipation of ***parent metiram*** in soil under aerobic biotransformation is attributable to hydrolysis, as such parent metiram is considered non-persistent	1723288
	Metiram Complex	13.6 d	132 d	FOMC	The ***metiram complex*** was determined to be non-persistent in soil under aerobic conditions. The DT_{50} was determined taking into consideration the extractable radioactivity and not the non-extractable residues. Non-extractable residues were determined to increase and ranged from 72.3 – 90.1%.	
Anaerobic Loamy sand	Minimal dissipation of metiram complex occurred under anaerobic conditions based on the mineralization data. A DT_{50} for metiram complex under anaerobic conditions was not determined.					1589664
Anaerobic loamy sand	Parent metiram	14.5 d	NC	SFO	This dissipation of ***parent metiram*** is affected by hydrolysis and is therefore, considered non-persistent under anaerobic soil conditions. The value was determined by the study author and could not be verified as the CS_2 data was not provided	1589663
	Metiram complex	24.7 d	82 d	FOMC	The ***metiram complex*** was determined to be non-persistent in soil under anaerobic conditions. The DT_{50} was determined taking into consideration the extractable radioactivity and not the non-extractable residues. Non-extractable residues were determined to increase and ranged from 29.8 – 50.2%.	
Mobility						
Soil Column Leaching	Sand	Kd = 0.58	Koc = 111		High mobility	1589679
	Sandy Loam		Kd = 1.68	Koc = 578	Medium – to –low mobility[1]	

Process	Substance	$t_{1/2}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA #
	Silt Loam		Kd = 6.17	Koc = 1061	Low mobility	
	Clay		Kd = 48.5	Koc = 1738	Low mobility	
Field Studies						
Terrestrial Field Dissipation (New York)	Metiram	135d	450 d	SFO	Moderately persistent[2]	1589667
	ETU	30 d	99 d	SFO	Slightly persistent	
Aquatic Environment						
Abiotic Transformation						
Hydrolysis	Metiram parent	33 h pH 5 45 h pH 7 75 h pH 9		SFO	Little information about this study available	1589671
	Metiram parent	Water Stable			Takes into consideration dissolution of parent metiram and hydrolysis ETU, EU, hydantoin, carbimid and two unidentified fractions were identified as transformation products. ETU was a major transformation product representing 81.5% of the total applied radioactivity	1589645
		pH 3 Stable				
		pH 5 Stable				
		pH 7 Stable				
		pH 9 Stable				
Hydrolysis – Metiram complex	EU (major @ pH 5, 7, 9)	pH 3 2.71 d	9.0 d	SFO	This portion of the study was designed to determine the kinetics of hydrolysis on the solution products	
		pH 5 – insufficient information to determine, non-detect at study termination				
		pH 7 – 9.7 d	32.1 d	SFO		
		pH 9 – 1.5 d	308000 d	FOMC		
	ETU (major @ pH 3, 5, 7, 9)	pH 3 – increasing at study termination				
		pH 5 – increasing at study termination				
		pH 7 – increasing at study termination				
		pH 9 – increasing at study termination				
	Carbimid (major @ pH 3, 5, 7 & 9)	pH 3 – 1.02 d	9.3 d	FOMC		
		pH 5 - < 1 d		Observed		
		pH 7 – 1.4 d	4.6 d	SFO		
		pH 9 – 0.9 d	3.2 d	SFO		
	EBIS (major @ pH 3)	pH 3 - < 1 d		Observed		
		pH 5 – not detected				
		pH 7 – not detected				
		pH 9 – not detected				
	UF (2)	pH 3 – increasing at study termination				

Process	Substance	$t_{½}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA #
		pH 5 – 3.2 d	202 d	FOMC		
		pH 7 stable at study termination				
		pH 9 – insufficient information to determine (< 11 d based on observation)				
	UF (1a)	pH 3 – not detected				
		pH 5 – only detected on day 12				
		pH 7 – insufficient information to determine				
		pH 9 - not detected				
	Hydantoin	pH 3 – insufficient information to determine				
		pH 5 – only detected on day 20				
		pH 7 – not detected				
		pH 9 – only detected on day 3				
Phototransformation water	Parent metiram	9.34 d	31 d	SFO	High pressure mercury light (relationship between the high pressure Hg lamp and natural sunlight could not be determined). Phototransformation in water is not considered an important route of dissipation for metiram.	1589657 1589650
Biotic Tansformation						
Aerobic Water/loamy sand sediment system A (pond)	Parent metiram	0.64 d	9.61 d	FOMC	The dissipation of ***parent metiram*** in soil under aerobic biotransformation is attribuatable to hydrolysis, as such, parent metiram is considered non-persistent. The major transformation product was ETU.	1589649
	Metiram Complex	178 d	590 d	SFO	The ***metiram complex*** was determined to be persistent in under aquatic aerobic conditions. Non-extractable residues were determined to increase from 7.3 to 27.4% at study termination.	
Aerobic Water/loamy sand sediment system B (small stream)	Parent metiram	0.17 d	9.01 d	FOMC	The dissipation of ***parent metiram*** in soil under aerobic biotransformation is attribuatable to hydrolysis, as such, parent metiram is considered non-persistent. The major transformation products were ETU, EBIS and CO_2	
	Metiram Complex	56.9 d	189 d	SFO	The ***metiram complex*** was determined to be moderately persistent in under aquatic aerobic conditions. Non-extractable residues were determined to range from 7.2 to 31.2%	

NC = not calculated
UF = unidentified fraction
[1] classified according to the classification of McCall et al (1981)
[2] classified according to the classification of Goring et al (1975)

McCall, J.P., D.A. Laskowski, R.L. Swann and J.J. Dishburger. (1981). Measurement of sorption coefficients of organic chemicals and their use in environmental fate analysis. Pages 89 - 109 *IN* Test protocols for environmental fate and movement of toxicants. Proceedings of a symposium. Association of Official Analytical Chemists. 94th Annual Meeting, October 21 - 22, 1980 Washington, DC.

Goring, C.A.I., D.A. Laskowski, J.H. Hamaker, and R.W. Meikle. (1975) Principles of pesticide degradation in soil. Pages 135-172 in (R. Haque and V.H. Freed, eds.) Environmental dynamics of pesticides. Plenum Press, New York.

Table 2 Toxicity to Non-Target Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
			Terrestrial Species		
Invertebrates					
Earthworm *(Eisenia fetida)*	Acute	Parent metiram	**LC_{50} > 1000 mg ai/kg soil**		1589683
			NOEC 400 mg ai/kg soil		
		Polyram WP (80% ai)	LC_{50} > 1000 mg EUP/kg soil		1639672
			NOEC 1000 mg EUP/kg soil		
Bee *(Apis mellifera L.)*	Oral	80% metiram EUP	**LD_{50} > 100 µg EUP/bee**	Relatively non-toxic[a]	1639673
Parasitic wasp *Aphidius rhopalosiphi* foliar-dwelling	Contact to dried residues on glass plates	BAS 222 28 F WG (70% metiram)	**LR50 >2.8 kg ai/ha**	4% corrected mortality at limit dose	1639694
Predatory mite *Typhlodromus pyri* foliar-dwelling	Contact to dried residues on glass plates	BAS 222 28 F WG (70% metiram)	**LR_{50} < 0.5 kg ai/ha**	100% mortality in all treatments	1639693
	Field exposure on grapevines in Germany 6 to 8 applications at 0.17 to 2.5 kg ai/ha in 10-14 day intervals	BAS 222 28 F WG (70% metiram)	**% reduction in population relative to control:** after 1st: 9% after 2nd: 16% after 3rd: 13% after 4th: 17% after 5th: 15% after 6th: 29% after 7th: 32% 1 week after 8th: 29% 4 weeks after 8th: 40%		1639680
			% reduction in population relative to control: after 1st: -21% after 2nd: -29% after 3rd: -5.8% after 4th: -48% after 5th: 33.6% after 6th: 9.3% after 7th: 43% 1 week after 8th: 69% 4 weeks after 8th: 49%		1639682
			% reduction in population relative to control: 1 week after 6th: 80% 4 weeks after 6th: 42%		1639684
			% reduction in population relative to control:		1639686

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
			1 week after 6th: 94% 4 weeks after 6th: 91%		
			% reduction in population relative to control: 1 week after 6th: 77% 4 weeks after 6th: 79%		1639690
			% reduction in population relative to control: 1 week after 6th: 41% 4 weeks after 6th: 70%		1639691
Beneficial spider *Pardosa* sp. ground-dwelling	Contact to dried residues on quartz sand	BAS 222 28 F WG (70% metiram)	**LR50 >5.6 kg ai/**	5% corrected mortality at limit dose	1639675
Birds					
Bobwhite quail (*Colinus virginianus*)	Acute	Technical metiram (95% ai)	**21-d LD_{50} > 2150 mg ai/kg bw**	Practically non-toxic; this study was conducted for longer than typical (usually 8 days)	1589705
	Dietary	Polyram 80 WP (80% ai)	8-d LC_{50} = 3712 mg ai/kg diet	Slightly toxic; only this highest dose showed mortality which was determined to be 50%, therefore LC_{50} was not determined statistically	1589703
			8-d LD_{50} = 5376 mg ai/kg bw [b]		
			NOEC = 800 mg ai/kg bw	Based on wing droop	
	Reproduction	BAS 222 28F (71% ai)	NOEC = 100 mg ai/kg diet	Endpoints affected: Higher number of cracked eggs, higher rate of early embryonic mortality, higher reate of " dead – in-shell" survivors, reduced number of eggs laid, reduced egg weight, reduced hatchability and reduced number of 14-d survivors	1589709
			NOEL = 8.5 (♂); 7.4 (♀) mg ai/kg bw [b]		
			LOEC = 300 mg ai/kg diet		
			LOEL = 25.6 (♂); 22.3 (♀) mg ai/kg bw [b]		
		Metiram premix (95%)	NOEC < 20 mg ai/kg diet	A significant increase in the number of infertile eggs were noted in the 20 and 100 mg ai/kg diet dose group which was not noticed in the 500 mg ai/kg diet dose group. Given that the other reproduction studies that were available for metiram were not tested below 50 mg ai/kg diet it is difficult to rule out the possibility of an inverted U non-monomeric dose	1589704
			NOEL < 2.09 mg ai/kg bw		
			LOEC = 20 mg ai/kg diet		
			LOEL = 2.09 mg ai/kg bw		

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
				response. As such, these endpoints were considered in the risk assessment.	
Mallard duck *(Anas platyrhnynccos)*	Dietary	Polyram 80 WP (80% ai)	LC_{50} > 3712 mg ai/kg bw	No mortality observed in this study at any dietary concentrations tested	1645224
			NOEC = 800 mg ai/kg bw	Based on body weight gain	
	Reproduction	Metiram premix (93% ai)	NOEC = 50 mg ai/kg diet	Endpoints affected: Reduced egg production, reducted mean egg weight, reduced fertility rate, reduced number of hatched ducklings, reduced number of 14-day old survivors and an increased rate of early embryonic deaths	1589706
			NOEL = 7.3 mg ai/kg bw ^{b}		
			LOEC = 300 mg ai/kg diet		
			LOEL = 44 mg ai/kg diet ^{b}		
			NOEC = 50 mg ai/kg diet	Endpoints affected: Reduction in the egg production; reduced mean egg weight; higher rate of early embryonic deaths; no hatched chicks at highest dose. Due to problems with egg shell thickness in this study these endpoints will not be considered in the risk assessment	1589710
			NOEL = 6.1 (♂); 7.4 (♀) mg ai/kg bw ^{b}		
			LOEC = 150 mg ai/kg diet		
			LOEL = 18.4 (♂); 22.1 (♀) mg ai/kg bw ^{b}		
Mammals					
Rat	Acute	metiram	**LD_{50} > 5000 mg/kg bw**	A variety of limit dose studies were available with doses ranging from 5 – 12000 mg/kg bw/day	
		ETU	LD_{50} = 545 – 1832 mg/kg bw (600 mg/kg bw for pregnant rats)		1570258, 1805631, 1805563, 1805536
Mouse		ETU	LD_{50} = 2400 – 4000 mg/kg bw		1805563, 1805631, 1570258
Rat	90-day dietary	metiram	13-wk NOEL = 6 (♂); 8 (♀) mg ai/kg bw/day 13-wk LC_{50} > 61(♂); **76 (♀) mg ai/kg bw/day**	Decrease thyroid uptake	
		ETU	NOEL = 1.7 mg/kg bw/day		1831764
Mice		ETU	NOEL = 1.7 mg/kg bw/day	hyperaemia of thyroid, increased thyroid wt., decreased thyroid binding globulin (TBG) T_3 and T_4	1570233

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
Rat	120-d dietary	ETU	NOEL = 2.5 mg/kg bw/day	↑ rel thyroid wt at ≥30 days, ↓ ^{131}I uptake at 24 h, slight hyperplasia of the thyroid gland.	1805536
Rat	Reproduction	metiram	HED decided that endpoint could not be determined. EPA set a provisional NOAEL for reproduction at **1.8mg/kg bw/day** based on decreased pregnancy rate in the F2 generation of the high dose.	Pregnancy rates were highly variable throughout the study – a new study is required. Given that maternal and fetal effects were noted in the developmental studies which indicate a decrease in pregnancy rates, the provisional NOAELs determined by the USEPA will be considered in the mammalian risk assessment until new information is available.	
	Developmental (oral gavage from gestational day 6 – 15)	metiram	Maternal LOAEL of 40 Developmental NOAEL of 80 mg/kg bw/day	**Maternal effects**: decreased body weight and body weight gain **Fetal effects** (developmental):decreased live litter size and litter weight, increased pre- and postimplantation loss.	
	Developmental (oral gavage gestational day 7 -19)	metiram	Maternal and Developmental NOAEL: 10 mg/kg bw/day	**Maternal effects**: decreased body weight, increase abortions **Fetal effects** (developmental): increased abortions, decrease fetal weight	
Rat		ETU	NOEL = Maternal: 40 Developmental: 5 (mg ai/kg bw/day)	@80 mg/kg bw/d: lethal to 9/11 dams. Fetal ≥5 mg/kg bw/d: ↑ in delayed ossification of the parietal bone (grps I and II). ≥10 mg/kg bw/d: (all grps): ↑ meningoencephalocele, meningorrhagia, meningorrhea, hydrocephalus, obliterated neural canal, abnormal pelvic limb posture with equinovarus, and short or kinked tail.	1805649, 1805557
		ETU	NOEL = Maternal: 35 Developmental: 15	Dams No maternal toxicity noted.	1805574

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
			(mg ai/kg bw/day)	Fetal ≥25 mg/kg bw/d: ↑ dilated brain ventricles (33.5%). @35 mg/kg bw/d: ↑ cranial meningocele and meningorrhea, severe hindlimb talipes, hydroureter and dilated ureter, and ↓ ossification of skull bones. 43.5% of fetuses had short or kinky tails, 93% had ELV, 33.5% had dumbell-shaped or bilobed vertebral centra.	
Rat, mice, hamster and guinea pigs		ETU	NOEL= 5 mg/kg bw/day rats	Maternal: @ 80 mg/kg bw/d: ↓ bwg and 25% mortality. DEV: ≥10 mg/kg bw/d: ↓ bw ≥20 mg/kg bw/d: ↑ hydrocephalus ≥40 mg/kg bw/d: ↓ ossification, ↑ encephalocele, kyphosis and digit defects. @ 80 mg/kg bw/d: ↑ mortality, edema, gross defects of the skeletal system and CNS. No apparent effects in hamsters or guinea pigs	1805604
Vascular plants					
Vascular plant	Seedling emergence Vegetative vigour		No data available – studies are required		
			Aquatic species		
Invertebrates *Daphnia magna*	Acute	metiram	48-h $EC_{50} > 1$ mg ai/L (nominal) 48-h $EC_{50} = 1.427$ mg ai/L (95% C.I :1.03 – 50.5 nominal)[1] 48-h $EC_{50} > 0.511$ mg ai/L ("effective concentration" based on median analytic recovery rate at 48 h)	Solutions were not filtered therefore measured endpoints determined may be overestimated Effect of concern: immobilization	1589687

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
			NOEC = 0.288 mg ai/L		
			48- h EC_{50} = 0.77 mg ai/L (nominal) 48- h EC_{50} = 0.25 mg ai/L ("effective concentration" based on median analytic recovery rate at 48 h) NOEC = 0.11 mg ai/L = 0.32 mg ai/L(nominal)	Highly toxic[c] Solutions were not filtered therefore endpoints determined may be overestimated Effect of concern: immobilization	1599692 1589691
			48-h EC_{50} = 2.55 mg ai/L (nominal) NOEC = 0 mg ai/L	Solutions were not analyzed therefore endpoints were based on nominal concentrations as such, the endpoints are likely overestimated. Effect of concern: immobilization	1639695
	99.6% ETU		48-h LC_{50} = 26900 µg a.i/L (measured)	Effect of concern: immobilization	1744702
	Chronic	metiram	21- d NOEC = 6.15 ug ai/L ("effective concentration" based on median analytic recovery rate at 48 h) **21- d NOEC = 25 ug ai/L (nominal)** 21- d LOEC = 12.3 ug ai/L	Solutions were not filtered prior to analysis therefore, endpoints determined may be overestimated. NOEC was based on # of live young. Effect of concern: # of live young	1589690
		ETU (% not reported)	21-d NOEC = 2000 µg a.i/L	Not reported	1744708
Fish Rainbow trout *(Oncorhynchus mykiss)*	Acute	metiram	**96- h LC_{50} = 0.76 mg ai/L (nominal concentration)** 96-h LC_{50}: 0.18 mg ai/L (filtered	Highly toxic[c]	1589698 1589697

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
			measured) 96-h LC_{50}: 0.45 mg ai/L (unfiltered measured)		
		99.6% ETU	96-h LC_{50} = >502000 µg a.i/L		1744702
	Chronic – Juvenile Growth	metiram	28-d NOEC = 0.044 mg ai/L LOEC = 0.14 mg ai/L LC_{50} = 0.18 mg ai/L	Metiram concentration in surface water of up to 0.04 mg ai/L will not have a negative impact on juvenile growth and survival. After multiple treatments with 0.14 mg ai/L only small effects were observed.	1589696
Bluegill sunfish *(Lepomis macrochirus)*	Acute	metiram	96-h LC_{50} > 160 mg ai/L	Study was not valid – will not be considered in RA	1589702
		metiram	96-h LC_{50} = 4.1 mg ai/L NOEC = 3.6 mg ai/L		1589701
		100% ETU	96-h LC_{50} = >990000 µg a.i/L		1619167
Algae Freshwater algae	Acute	metiram	**72-h EC_{50} = 0.054 mg ai/L (nominal concentration)** NOEC = 0.01 mg ai/L	Highly toxic[c]	1589711
		metiram	96-h EC_{50} = 0.27 mg ai/L NOEC = 0.05 mg ai/L		1589712
Vascular plant	No data were available for metiram complex				
Duckweed (*L. gibba*)	Acute	100% ETU	7-d EC_{50} =>960000 µg a.i/L NOEC = 960000 µg a.i/L (nominal)		1619169
Amphibians[1]	Acute	metiram	**96- h LC_{50} = 0.76 mg ai/L (nominal concentration)**	Highly toxic[c]	1589698 1589697
	Acute	ETU (purity not reported)	28-d NOEC = 10000 µg a.i./L		1744712
	Chronic	ETU (purity not reported)	90-d NOEC = 10000 µg a.i./L (Developmental effects) 90-d NOEC =		1722137

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA #
			1000 µg a.i./L (Histological alterations (thyroid)		1744709
Marine species					
Crustacean	Acute	No data were available for metiram			
Mysid shrimp (*Mysidopsis bahia*)	Acute	100% ETU	96-h LC_{50} =9200 µg a.i/L NOEC = 6400 µg a.i/L (mean measured)		1616165
Eastern oysters (*Crassostrea virginica*)		100% ETU	96-h EC_{50} = >110000 µg a.i/L NOEC = 42 000µg a.i/L (mean measured)		1619166
	Chronic	No data were available			
Mollusc	Acute	No data were available			
	Chronic	No data were available			
Salmonid	Acute	No data were available			
Fish Sheepshead minnow (*Cypronodon variegates*)	Acute	100% ETU	96-h LC_{50} = >900 µg a.i/L NOEC = 900 µg a.i/L (mean measured)		1619168
Marine alga	Acute	No data were available			

a Atkins et al. (1981) for bees and USEPA classification for others, where applicable

[b] 8-d LD_{50}, NOEL, LOEL calculated using (concentration in diet × FIR)/BW; FIR = mean food ingestion rate reported in study, BW = mean body weight reported in study

[c] USEPA's toxicity classification

[1] Endpoints from fish used as surrogate

Values in bold used in risk assessment

Atkins EL; Kellum D; Atkins KW. 1981. Reducing pesticide hazards to honey bees: mortality prediction techniques and integrated management techniques. Univ Calif, Div Agric Sci, Leaflet 2883. 22 pp

Table 3 Screening Level Risk Assessment on Non-Target Terrestrial Species Other Than Birds And Mammals

Organism	Exposure Type	Endpoint value	EEC[2]	RQ[3]	LOC[4] exceeded
Invertebrates					
Earthworm	Acute	LC_{50} > 1000 mg ai/kg soil	8.1 mg ai/kg soil	<0.01	No
Bee	Oral	LD_{50} > 112 mg ai/kg / ha[1]	15.8 kg ai/ha[5]	<0.14	No
Parasitic wasp *Aphidius rhopalosiphi* foliar-dwelling	Contact to dried residues on glass plates	LR50 >2.8 kg ai/ha	10.7 kg ai/ha	<3.8	Likely
Predatory mite *Typhlodromus pyri* foliar-dwelling	Contact to dried residues on glass plates	LR_{50} <0.5 kg ai/ha	10.7 kg ai/ha	>21	Yes

Organism	Exposure Type	Endpoint value	EEC[2]	RQ[3]	LOC[4] exceeded
Beneficial spider *Pardosa* sp. ground-dwelling	Contact to dried residues on quartz sand	LR_{50} >5.6 kg ai/ha	18.2 kg	<3.3	Likely

[1] Toxicity in µg/bee converted to the equivalent kg a.i./ha using a conversion factor of 1.12 (Atkins *et al.*, 1981)

[2] The screening level Estimated Exposure Concentration (EEC) is calculated for the apple scenario assuming four applications of 4.8 kg ai/ha with a minimum interval of 7 days (default foliar half-life of 10 days, soil DT50 of 135 days based on field dissipation in New York, PMRA 1589667).

[3] Risk Quotient (RQ) = EEC/toxicity endpoint value

[4] Level of Concern (LOC) is 2 for *T.pyri* & *A.rhopalosiphi* toxicity values from glass plate tests only; LOC is 1.0 for all remaining organisms.

Table 4 Screening Level Risk Assessment for Birds and Mammals Using Maximum Kenaga Values

Organism	Toxicity (mg ai/kg bw/d)	Feeding Guild (food item)	EDE (mg ai/kg bw)	RQ
Small Bird (0.02 kg)				
Acute	215.00	Insectivore (small insects)	538.85	2.51
Reproduction	2.09	Insectivore (small insects)	538.85	257.82
Medium Sized Bird (0.1 kg)				
Acute	215.00	Insectivore (small insects)	420.51	1.96
Reproduction	2.09	Insectivore (small insects)	420.51	201.20
Large Sized Bird (1 kg)				
Acute	215.00	Herbivore (short grass)	438.79	2.04
Reproduction	2.09	Herbivore (short grass)	438.79	209.95
Mammal				
Small Mammal (0.015 kg)				
Acute	500.00	Insectivore (small insects)	309.93	0.62
Reproduction	1.80	Insectivore (small insects)	309.93	172.18
Medium Sized Mammal (0.035 kg)				
Acute	500.00	Herbivore (short grass)	971.00	1.94
Reproduction	1.80	Herbivore (short grass)	971.00	539.45
Large Sized Mammal (1 kg)				
Acute	500.00	Herbivore (short grass)	518.84	1.04
Reproduction	1.80	Herbivore (short grass)	518.84	288.24

Table 5 Screening Level Risk Assessment For Aquatic Non-Target Organisms

Crop			**Apples**			**Sugar Beets**		
Organism	**Exposure Type**	**Endpoint value**	**EEC^2: 2.31 EEC^1: 12.29**	**RQ**	**LOC exceeded**	**EEC^1: 0.444 EEC^2: 2.368**	**RQ**	**LOC exceeded**
Freshwater Organisms								
Daphnia magna	Acute (unfiltered)	48-h $EC_{50}/2$ =0.385 mg ai/L	2.31mg ai/L	6.0	Yes	2.368 mg ai/L	1.2	Yes
	Repro	NOEC = 0.025 mg ai/L	2.31mg ai/L	92.2	Yes	2.368 mg ai/L	17.8	Yes
Rainbow trout	Acute (filitered)	96-h $LC_{50}/10$ =0.76 mg ai/L	2.31mg ai/L	30.3	Yes	2.368 mg ai/L	5.8	Yes
Ankistrodesmus bibraianus	Acute (filtered)	$EC_{50}/2$ = 0.027 mg ai/L	2.31mg ai/L	85.4	Yes	2.368 mg ai/L	16.4	Yes
Amphibians								
Amphibians	Acute	96-h $LC_{50}/10$ = 0.018 mg ai/L^3	12.62 mg ai/L	161.8	Yes	0.444 mg ai/L	31.2	Yes

Note: All the toxicity concentrations and EECs are mg a.i./L.

^{1}: EEC in 15cm water depth (amphibians)

^{2}: EEC in 80cm water depth (fish and other organisms)

^{3}: toxicity end point of fish were used as a surrogate for amphibian RA

Aquatic invertebrates, algae and plants (acute): RQ = EEC/(EC50 ÷ 2)

All other aquatic organisms: EEC/(LC50 ÷ 10)

Chronic risk: NOEC

Table 6 Refined Reproduction Risk Assessment for Birds and Mammals Using Mean Kenaga Values

Organism	**Endpoint value**	**Feeding Guild**	**On field**				**Off-field**			
			EDE^1	**RQ^2**	**LOC^3 exceeded**	**% contaminated food^4**	**EDE**	**RQ**	**LOC exceeded**	**% contaminated food to reach LOC**
Apples										
Bird weight: 20 g	21 wk NOEL = 2.09 mg ai/kg bw/day	Insectivore	300.5	143.7	Yes	1	222.4	106	Yes	1
		Granivore	64.2	30.7	Yes	3	47.5	23	Yes	4
		Frugivore	128.5	61.5	Yes	2	95.1	46	Yes	2
Bird weight: 100 g		Insectivore	234.5	112	Yes	1	173.5	83	Yes	1
		Granivore	50.1	24	Yes	4	37.1	18	Yes	6
		Frugivore	100.3	48	Yes	2	74.2	36	Yes	3

Organism	Endpoint value	Feeding Guild	On field				Off-field			
			EDE[1]	RQ[2]	LOC[3] exceeded	% contaminated food[4]	EDE	RQ	LOC exceeded	% contaminated food to reach LOC
Bird weight: 1000g		Insectivore	14.6	7	Yes	14	10.8	5	Yes	19
		Granivore	68.5	7	Yes	14	50.7	5	Yes	19
		Frugivore	14.6	14	Yes	7	10.8	10.4	Yes	10
		Herbivore (short grass)	155.8	75	Yes	1	115.3	55	Yes	2
		Herbivore (long grass)	87.5	42	Yes	2	64.7	31	Yes	3
		Herbivore (forage crops)	134.2	64	Yes	2	99.3	48	Yes	2
		Herbivore (leafy foliage)	273.4	131	Yes	1	202.3	97	Yes	1
Mammal weight: 15 g	NOEL = 1.8 mg ai/kg bw	Insectivore (small insects)	172.8	96.0	Yes	1.0	127.9	71.1	Yes	1.4
		Granivore	37.0	20.5	Yes	4.9	27.3	15.2	Yes	6.6
		Frugivore	73.9	41.1	Yes	2.4	54.7	30.4	Yes	3.3
Mammal weight: 35 g	Acute: LD_{50}/10 > 500 mg ai/kg bw	Herbivore (leafy foliage)	605.0	1.2	Yes	82.6	447.7	0.9	No	
	NOEL = 1.8 mg ai/kg bw	Insectivore (small insects)	151.5	84.2	Yes	1.2	112.1	62.3	Yes	1.6
		Granivore	32.4	18.0	Yes	5.6	24.0	13.3	Yes	7.5
		Frugivore	64.8	36.0	Yes	2.8	47.9	26.6	Yes	3.8
		Herbivore (short grass)	184.3	102.4	Yes	1.0	136.4	75.8	Yes	1.3
		Herbivore (long grass)	103.4	57.5	Yes	1.7	76.5	42.5	Yes	2.4
		Herbivore (forage crops)	158.7	88.2	Yes	1.1	117.4	65.2	Yes	1.5
		Herbivore (leafy foliage)	323.3	179.6	Yes	0.6	239.2	132.9	Yes	0.8

Organism	Endpoint value	Feeding Guild	On field				Off-field			
			EDE[1]	RQ[2]	LOC[3] exceeded	% contaminated food[4]	EDE	RQ	LOC exceeded	% contaminated food to reach LOC
Mammal weight: 1kg	NOEL = 1.8 mg ai/kg bw	Insectivore (large insects)	17.3	9.6	Yes	10.4	12.8	7.1	Yes	14.1
		Granivore	17.3	9.6	Yes	10.4	12.8	7.1	Yes	14.1
		Frugivore	34.6	19.2	Yes	5.2	25.6	14.2	Yes	7.0
		Herbivore (short grass)	184.3	102.4	Yes	1.0	136.4	75.8	Yes	1.3
		Herbivore (long grass)	103.4	57.5	Yes	1.7	76.5	42.5	Yes	2.4
		Herbivore (forage crops)	158.7	88.2	Yes	1.1	117.4	65.2	Yes	1.5
		Herbivore (leafy foliage)	323.3	179.6	Yes	0.6	239.2	132.9	Yes	0.8
Beet										
Bird weight: 20 g	21 wk NOEL = 2.09 mg ai/kg bw/day	Insectivore	81.7	39	Yes	3	4.9	2	Yes	43
		Granivore	17.5	8	Yes	12	1.0	0.5	No	
		Frugivore	34.9	17	Yes	6	2.1	1	No	
Bird weight: 100 g		Insectivore	63.8	31	Yes	3	3.8	2	Yes	55
		Granivore	13.6	7	Yes	15	0.8	0.4	No	
		Frugivore	27.3	13	Yes	8	1.6	0.8	No	
Bird weight: 1000g		Insectivore	3.9	2	Yes	53	0.2	0.1	No	
		Granivore	18.6	9	Yes	53	1.1	0.5	No	
		Frugivore	3.9	2	Yes	26	0.2	0.1	No	
		Herbivore (short grass)	42.4	20	Yes	5	2.5	1.2	Yes	82
		Herbivore (long grass)	43.8	11	Yes	9	1.4	0.7	No	
		Herbivore (forage crops)	36.5	18	Yes	6	2.2	1.0	No	95
		Herbivore (leafy foliage)	74.3	36	Yes	3	4.5	2	Yes	47
Mammal weight: 15 g	NOEL = 1.8 mg ai/kg bw	Insectivore (small insects)	47.0	26.1	Yes	3.8	2.8	1.6	Yes	63.8
		Granivore	10.0	5.6	Yes	17.9	0.6	0.3	No	
		Frugivore	20.1	11.2	Yes	9.0	1.2	0.7	No	
Mammal weight: 35 g	NOEL = 1.8 mg ai/kg bw	Insectivore (small insects)	41.2	22.9	Yes	4.4	2.5	1.4	Yes	72.8
		Granivore	8.8	4.9	Yes	20.4	0.5	0.3	No	
		Frugivore	17.6	9.8	Yes	10.2	1.1	0.6	No	

Organism	Endpoint value	Feeding Guild	On field				Off-field			
			EDE[1]	RQ[2]	LOC[3] exceeded	% contaminated food[4]	EDE	RQ	LOC exceeded	% contaminated food to reach LOC
		Herbivore (short grass)	50.1	27.8	Yes	3.6	3.0	1.7	Yes	59.9
		Herbivore (long grass)	28.1	15.6	Yes	6.4	1.7	0.9	No	
		Herbivore (forage crops)	43.2	24.0	Yes	4.2	2.6	1.4	Yes	69.5
		Herbivore (leafy foliage)	87.9	48.8	Yes	2.0	5.3	2.9	Yes	34.1
Mammal weight: 1kg	NOEL = 1.8 mg ai/kg bw	Insectivore (large insects)	4.7	2.6	Yes	38.2	0.3	0.2	No	
		Granivore	4.7	2.6	Yes	38.2	0.3	0.2	No	
		Frugivore	9.4	5.2	Yes	19.1	0.6	0.3	No	
		Herbivore (short grass)	50.1	27.8	Yes	3.6	3.0	1.7	Yes	
		Herbivore (long grass)	28.1	15.6	Yes	6.4	1.7	0.9	No	
		Herbivore (forage crops)	43.2	24.0	Yes	4.2	2.6	1.4	Yes	69.5
		Herbivore (leafy foliage)	87.9	48.8	Yes	2.0	5.3	2.9	Yes	34.1

[1] Estimated Daily Exposure (EDE) = FIRww/BW*EEC Estimated Environmental Concentration (EEC) in fresh diet (mg a.i./kg fresh weight diet); the off-field EEC was used to further characterize exposure estimates. For off-field EECs, the following deposition rates were used: 74% spray deposition: airblast application with a fine droplet spray quality (ASAE classification).Food Ingestion Rate of indicator species in wet weight (FIR); Bodyweight (BW) (kg)

For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:

Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$

All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$

All Mammals Equation: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$

[2] Risk Quotient (RQ) = exposure/toxicity

[3] Level of Concern (LOC)

[4] Percentage of contaminated food needed to trigger reproductive effect

Shaded cells indicate that the RQ exceeds the LOC, triggering a refined risk assessment and further characterization where possible.

Table 7 Temporal Chronic Risk as a Result of Metiram on Avian and Mammalian Food Items Based on Kenaga Maximum and Mean Residues

Crop	Number of Days metiram Exposure Exceed Birds Chronic NOEL		Number of Days metiram Exposure Exceed Mammalian Chronic NOEL	
	On-field	Off-field	On-field	Off-field
Based on Maximum Kenaga Residues				
Apple	72 - 119	67 - 115	76 - 126	72 - 120
Grape	46 - 93	41 - 89	52 – 100	48 - 95
Potato	104 – 151	63 – 111[1]	108 - 156	32 – 115[1]
Beet	34 - 82	5 - 41	39 - 86	1 - 46
Carrot	58 - 105	11 - 65	62 - 110	1 - 69
Tomato, Asparagus, Celery	63 - 110	1 - 70	68 - 115	11 - 74
Based on Mean Residues				
Apple	61 - 105	57 - 100	66 - 108	61 - 104
Grape	35 - 79	31 - 74	41 - 84	37 - 79
Potato	93 - 137	63 – 95[1]	87 - 135	38 - 140[1]
Beet	24 – 67	2 - 27	28 – 71	2 - 30
Carrot	47 - 91	5 - 50	52 - 94	1 - 53
Tomato, Asparagus, Celery	52 - 95	19 - 55	57 - 99	7 - 59

[1] = Ground application

Table 8 Refined Risk Assessment For Non-Target Aquatic Organisms Using Percent Drift Deposition for Applications

Organism	Exposure Type	Endpoint value (mg ai/L)	Use scenario	EEC[a] Exposure from drift	RQ[b]	LOC exceeded
Airblast application (74% spray deposition)						
Daphnia magna	Acute	48-h EC_{50}/2 =0.385	Apple	1.71	4.4	Yes
			grape	0.44	1.1	Yes
	Reproduction	NOEC = 0.025	Apple	1.71	68.2	Yes
			grape	0.43	17.3	Yes
Rainbow trout (*Onchorhynchus mykiss*)	Acute	96-h LC_{50}/10 =0.076	Apple	1.71	22.4	Yes
			grape	0.43	5.7	Yes
Green Algae (*Ankistrodesmus bibraianus*)	Acute	EC_{50}/2 = 0.027	Apple	1.71	63.2	Yes
			grape	0.43	16	Yes
Amphibians	Acute	96-h LC_{50}/10 = 0.076	Apple	9.10	119.7	Yes
			grape	2.30	30.33	Yes
Ground application (6% spray deposition)						
Daphnia magna	Acute	48-h EC_{50}/2 =0.385	Sugar beet	0.027	0.07	No
			Potato	0.12	0.32	No
	Reproduction	NOEC = 0.025	Sugar beet	0.027	1.07	Yes
			Potato	0.12	5.0	Yes
Rainbow trout (*Onchorhynchus mykiss*)	Acute	96-h LC_{50}/10 =0.076	Sugar beet	0.027	0.4	No
			Potato	0.12	1.63	Yes
Green Algae (*Ankistrodesmus bibraianus*)	Acute	EC_{50}/2 = 0.027	Sugar beet	0.027	0.99	No
			Potato	0.12	4.6	Yes
Amphibians	Acute	96-h LC_{50}/10 = 0.076	Sugar beet	0.14	1.9	Yes
			Potato	0.7	8.7	Yes

Organism	Exposure Type	Endpoint value (mg ai/L)	Use scenario	EEC[a] Exposure from drift	RQ[b]	LOC exceeded
Aerial application (23% spray deposition)						
Daphnia magna	Acute	48-h $EC_{50}/2$ = 0.385	Potato	0.48	1.2	Yes
	Reproduction	NOEC = 0.025	Potato	0.48	19.0	Yes
Rainbow trout (*Onchorhynchus mykiss*)	Acute	96-h $LC_{50}/10$ =0.076	Potato	0.48	6.3	Yes
Green Algae (*Ankistrodesmus bibraianus)*	Acute	$EC_{50}/2$ = 0.027	Potato	0.48	17.5	Yes
Amphibians	Acute	96-h $LC_{50}/10$ = 0.076	Potato	2.53	33.3	Yes

[a] 74% spray deposition: early season spray drift at one metre downwind resulting from airblast applications 6% spray deposition ground applications 23% spray deposition from aerial application

[b] Risk Quotient = Exposure/Toxicity. Shaded cells indicate that the screening level risk quotient exceeds the level of concern (LOC = 1)

Table 9 Comparison of Risk Quotients from Refined Risk Assessment Using the Current Registered Application RATEs and the USEPA Recommended Application Rates

Organism	Range of risk quotient determined from Current rate		Range of risk quotient determined from USEPA recommended rate		Percentage risk reduction	
Terrestrial						
Apples	**4800 g ai/ha × 4 × 7**		**4035 g ai/ha × 3 × 7**			
	On-field	Off-field	On-field	Off-field	On-field	Off-field
Birds 20 g	30.7 – 143.8	23 -106	23.1 – 108.2	17- 80	25.1 – 24.8	26.1 – 24.5
100 g	24 – 112.2	18-83	18.1 – 84.5	13 - 62.5	24.6 – 24.7	27.8 – 24.7
1000 g	7 – 130.8	5-97	5.3 – 98.4	4 - 73	24.3 – 24.8	20 – 24.8
Mammals 15g	20.5 - 96	15.2 – 71.1	15.5 – 72.3	11.4 – 53.5	24.4 – 24.7	25 – 24.8
35g	18 – 179.6	13.3 – 132.9	13.5 – 135.2	10 - 100	25 - 24.7	24.8 – 24.8
1000g	19.2 - 179.6	7.1 – 132.9	7.2 – 135.2	5.4 - 100	62.5 – 23.9	23.9 – 24.8
Potatoes (aerial application)	**1800 g ai/ha × 10 × 5**		**1800 g ai/ha × 6 × 5**			
Birds 20 g	17.1 – 80.1	3.9 -18.4	15.5 – 72.3	3.6 – 16.6	9.4 – 9.7	7.8 -9.8
100 g	13.4 – 62.5	3.1 – 14.4	12.1 – 56.4	2.8 – 13.0	9.7 – 9.8	9.7 – 9.7
1000 g	3.9 – 72.8	1.8 – 16.8	3.5 – 65.8	1.6 – 15.2	10.3 – 9.6	11.1 – 9.5
Mammals 15g	11.4 – 53.5	2.6 – 12.3	10.3 – 48.3	2.4 – 11.1	9.7 – 9.7	7.7 – 9.8
35g	10 - 100	2.3 - 23	9.1 – 90.3	2.1 – 20.8	9 – 9.7	8.7 – 9.7
1000g	5.4 - 100	1.2 - 23	4.8 – 90.3	1.1 – 20.8	11.1 – 9.7	8.3 – 9.7

Organism	Range of risk quotient determined from Current rate		Range of risk quotient determined from USEPA recommended rate		Percentage risk reduction	
Aquatic Spray Drift						
Apples (airbalst application)						
Daphnia magna (acute)	4.4		2.8		36.4	
Daphnia magna (chronic)	68.2		43.6		36.1	
Rainbow trout (acute)	22.4		14.3		36.2	
Green Algae (acute)	63.2		40.4		36.1	
Amphibian (acute)	119.7		76.5		36.1	
Potatoes (aerial application)						
Daphnia magna (acute)	1.2		0.77			
Daphnia magna (chronic)	19.0		11.8		37.9	
Rainbow trout (acute)	6.3		3.9		38.1	
Green Algae (acute)	17.5		11		37.1	
Amphibian (acute)	33.3		20.8		37.5	
Potatoes (ground application)						
Daphnia magna (acute)	0.32		0.2			
Daphnia magna (chronic)	5.0		3.1		38	
Rainbow trout (acute)	1.6		1.02		36.3	
Green Algae (acute)	4.6		2.9		37	
Amphibian (acute)	8.7		5.4		37.9	
Aquatic Run-off						
	Apples	Potatoes	Apples	Potatoes	Apples	Potatoes
Daphnia magna (acute)	0.39	1.7	0.24	1.07		
Daphnia magna (chronic)	5.2	23.2	2.9	14.12	44	39.5
Rainbow trout (acute)	1.9	8.1	1.1	5.2		
Green Algae (acute)	5.6	24.1	3.4	15.3	39.3	36.5
Amphibian (acute)	5.4	19.3	3.3	12.17	38.9	36.8

Table 10 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	No: 0.6-9.1 days (parent) 1.9– 13.6 days (metiram complex)
	Water	Half-life ≥ 182 days	Yes: 453 days in natural waters
	Sediment	Half-life ≥ 365 days	No: aerobic half-life = 178 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (< 1×10^{-7} Pa @ 20° C) and Henry's Law Constant (<5.4×10^{-3} Pam^3/mole @ 20° C).

TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**	**Active Ingredient Endpoints**
Bioaccumulation[4]	Log $K_{OW} \geq 5$	No: 0.19 – 1.92
	BCF $\geq$ 5000	not available
	BAF $\geq$ 5000	not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet TSMP Track 1 criteria.

Appendix X Monitoring Data

EBDC fungicides are very short-lived in the environment and are not expected to persist in surface waters or reach groundwater because they hydrolyze rapidly into their complexes. The complex comprises of a suite of chemical species including ETU - a common transformation product of all the EBDCs. ETU is highly water soluble and may reach both surface and groundwater in the right conditions. Therefore, the monitoring data for ETU and EBDC complexes will be used in the assessment of exposure concentrations in water for all EBDCs.

A search for Canadian water monitoring data on EBDC fungicides such as metiram, mancozeb, nabam and their common transformation product ETU was undertaken. The Federal Provincial and Territorial representatives from all of the provinces and territories in Canada were contacted, requesting water monitoring data for EBDC fungicides. In addition, requests were submitted to Environment Canada, the Department of Fisheries and Oceans and the drinking water sub-committee through Health Canada. A response was received by most provinces and territories indicating that either monitoring data were not available or the available data were submitted.

The search resulted in a number of datasets in which either the individual parent compounds, EBDC (dithiocarbamates) or ETU were included in the analyte list. There were recorded detections of ETU and EBDCs. In some cases, the parent compounds were detected, but a high level of uncertainty and loss of sensitivity in the analytical methods made the results questionable. There was no detection of metiram.

American databases were searched for detections of all the EBDCs and ETU. No data were available from the United States' Geological Survey National Water Quality Assessment program (NAWQA), for either groundwater or surface water, nor from the Six Year Review of National Drinking Water Regulations, as part of the United States' National Contaminant Occurrence Database (NCOD). However, in 2001-2003, the USEPA conducted a targeted monitoring study in seven states chosen to represent the high historic EBDC use areas in the United States. Metiram was not detected.

A summary of the findings is presented in Table 2.

Table 1 Summary of Available Monitoring Studies and Data

Data Source	Location	EBDC tested	Min detection or detection limit (µg/L)	# of samples tested	# of samples with detections	%Detection Frequency	Absolute Maximum concentration (µg/L)
PMRA 1345897	Maritimes surface and groundwater (Prince Edward Island) 1999	Mancozeb	N/A	N/A	N/A	N/A	6.9; 20
	2000	Mancozeb	N/A	N/A	N/A	N/A	1.40
PMRA 1726638	PEI (municipal, institutional & private water supply) 2006	EBDC complexes	N/A	124	N/A	8-43	34-53

Data Source	Location	EBDC tested	Min detection or detection limit (µg/L)	# of samples tested	# of samples with detections	%Detection Frequency	Absolute Maximum concentration (µg/L)
PMRA 1726642	2007	EBDC complexes	N/A	N/A	10	10-50	16-60
PMRA 1346006	Canada /PEI Water Management Agreement 1987	Mancozeb	25	21	4	19	32
PMRA 1737520	PEI (groundwater)	Metiram & Mancozeb	100	101	N/D	N/D	N/D
PMRA 1311124	Alberta (surface water)	Metiram & Mancozeb	10	20	N/D	N/D	N/D
PMRA 1307578	Quebec (Déversant du Lac stream) close to Apple orchard 1995	ETU	N/A	N/A	N/A	12	1.1
	1996	ETU	1	N/A	N/A	N/A	2.3
PMRA 1311119, 1311120	Quebec (private water wells located in potato growing areas) 2000-2001	ETU	N/A	51	N/D	N/D	N/D
EPA RED for metiram, 2005	EPA targeted monitoring study in seven USA states of high historic EBDC use 2001-2003	ETU (in public drinking water well in Lee County, Florida)	N/A	N/A	N/A	N/A	0.21
		ETU (in private water well in Apple growing area of New York)	N/A	N/A	N/A	N/A	0.57

N/D = Not detected
N/A = Not available

Modelling results

Table 2 Level 1 and Level 2 estimated environmental concentrations of ETU in potential drinking water sources

Modelling Level	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Level 1	0.36	0.35	75	8.6	74	19
Level 2	N/A[5]	N/A	16	2.9	27	7.2

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peak concentrations
4 90th percentile of yearly average concentrations
5 Not applicable

References

Chemistry

A. Studies/Information submitted by the registrant (Unpublished)

PMRA Document Number	Reference
1253162	1992, Product Chemistry-Product Identity and Composition, Beginnng Materials and Manufacturing Process and Discussion of the Formation of impurities of Polyram DF (BAS 222 228F), DACO: 2.11.1,2.11.2,2.11.3,2.11.4
1452338	2007, Statement of Product Specification Form, DACO: 0.1.6003
1348820	1994, Summary report: Composition of five batches of Metiram TK 85 (formerly called Metiram Premix), DACO: 2.12.1
1348831	1994, Preliminary analysis: Five batches of Metiram Premix, DACO: 2.13.3,2.13.4
1348824	2003, Final Report: Five Batches of 'Polyram DF', DACO: 2.13.1
1348830	1994, Preliminary analysis: Five Batches of Metiram Premix (BAS 222 29 F), DACO: 2.13.3
1253164	1992, Analaysis and Certification of Product Ingredients and Validation of Analytical Methods for Polyram DF (BAS 222 28F), DACO: 2.13.3

Value

B. Additional Information Considered

Published Information

PMRA Document Number	Reference
2107100	2004. Crop Profile for Apple in Canada. Pesticide Risk Reduction program, Pest Management Centre, Agriculture and Agri-Food Canada. DACO: 10.6
2097630	2005. Crop Profile for Potato in Canada. Pesticide Risk Reduction program, Pest Management Centre, Agriculture and Agri-Food Canada. DACO: 10.6

2097631 2008. Apple Fungicide – Resistance Management. British Columbia Ministry of Agriculture and Lands. http://www.al.gov.bc.ca/cropprot/tfipm/apple_fungicides.htm. DACO: 10.6

2097632 Canadian Horticultural Council. 2010, Crop Profile for Apple in Canada. Pesticide Risk Reduction Program, Pest Management Centre, Agriculture and Agri-Food Canada. DACO: 10.6

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2097635 Solymar, B. and M. Appleby. 2005, Apple Scab. Ontario Ministry of Agriculture, Food and Rural Affairs. http://www.omafra.gov.on.ca/english/crops/facts/apscab.htm. DACO: 10.6

2097636 Wukasch, R.T. 2009. Diseases of asparagus. Ontario Ministry of Agriculture, Food and Rural Affairs. http://www.omafra.gov.on.ca/english/crops/facts/82-045.htm. DACO: 10.6

Toxicology

A. Studies/Information submitted by the Registrant (Unpublished)

Metiram

PMRA Document Number	Reference
1589583	1991. 52-week oral toxicity (feeding) study with metiram premix 95% in the dog, DACO: 4.3.2
1230460	1983. Acute Inhalation tox (LC_{50}) - metiram tech as a dust aerosol - 4 hour exposure - rats, DACO: 4.2.3
1228700	1975. Acute oral tox - metiram - rat, DACO: 4.2.1
1589544	1974. Acute oral toxicity of the technical active ingredient Metiram to the rat, DACO: 4.2.1
1230451	1977. Ames test for metiram , DACO: 4.5.4
1230450	1979. Dominant lethal assay of metiram tech in the male mouse, DACO: 4.5.4, 4.5.8
1230462	1979. Effect of metiram technical on pregnancy in the rat, DACO: 4.5.1, 4.5.2
1230447	1981. Effect of metiram technical on reproductive function of multiple generations in the rat, DACO: 4.5.1, 4.5.2
1589536	1972. Evaluation of metiram in the C3H-10T ½ cell system for transformation and promotion activities, DACO: 4.1, 4.8
1589538	1984. Evaluation of metiram tech. in the rat primary hepatocyte unscheduled DNA synthesis assay, DACO: 4.5.8, 4.1
1831830	1996. Genotoxic Effects of pesticides - Journal of Environmental Pathology, Toxicology and Oncology, Vol 15, No. 2-4, p. 75-78, DACO: 4.5.8
1228704	1974. Irritant Effect - metiram - rabbit, DACO: 4.2.4, 4.2.5
1570258	1993. Metiram - (active ingredient) oral toxicity study in beagle dogs (dietary intake for 4 weeks) in JMPR Review 1993, DACO: 12.5.4
1589582	1977. Metiram - toxicity to rats in dietary administration for 13 weeks followed by a 6 week withdrawal period, DACO: 4.3.1, 4.4.4
1230445	1979. Metiram - tumorgenicity to mice in long term dietary admin - cont'd from roll # 79 (appendices cont'd in batches 2-5), DACO: 4.4.1, 4.4.2

1228711 1979. Metiram - tumorgenicity to mice in long term dietary administration, final report, BSF 198/78265, (includes Batches 79, 80, 81, 82, 83, 854 And 85) cont'd on roll # 80, DACO: 4.4.1

1230454 1981. Metiram toxicity and tumorgenicity in prolonged dietary administration to the rat, WNT 77/951, (includes Batches 18 To 50), DACO: 4.4.1,4.4.2

1230456 1981. Metiram toxicity and tumorgenicity in prolonged dietary administration to the rat, WNT77/951, DACO: 4.4.1, 4.4.2

1589568 1985. Mutagenicity evaluation of metiram technical K38/33A in an *in vitro* sister chromatid exchange assay in Chinese hamster ovary (CHO) cells, DACO: 4.5.5, 4.4.2

1589569 1986. Mutagenicity evaluation of Metiram technical K38/33A in the rat bone marrow cytogenetic assay, DACO: 4.4.3

1589570 1985. Mutagenicity evaluation of Metiram technical K38/33A in the rat bone marrow cytogenetic assay, DACO: 4.4.3

1570233 1992. NTP tech report on the perinatal toxicity and carcinogenesis studies of ETU in F344/N rats and $B_6C_3F_1$ mice, DACO: 4.4.2, 4.4.3

1228706 1979. Oral toxicity study in rhesus monkeys - repeated dosage for 26 weeks with recovery period - metiram , BSF 267/78263, (includes Batches 74 And 75), DACO: 4.3.1

1589596 1990. Report on point mutation test carried out on CHO cells (HGPRT locus) with the test substance Metiram premix 95% with $B_6C_3F_1$ mice microsomal fraction, DACO: 4.8

1209690 1987. Report on the acute dermal irritation to the eye of the white rabbit, DACO: 4.6.4

1209689 1987. Report on the acute dermal irritation/corrosivity to the intact dorsal skin of the white rabbit, DACO: 4.6.4

1589603 1980. Report on the determination of the acute inhalation toxicity LC_{50} of Metiram techn. with 2% ETU as dust, aerosol after 4-hour exposure in Sprague-Dawley rats, DACO: 4.2.3,4.8

1589552 1990. Report on the sister chromatid exchange assay in bone marrow cells of the Chinese hamster with Metiram premix 95%, DACO: 4.2.3

1589542 1981. Report on the study of the acute oral toxicity of 'metiram technical grade' in the rat, 1981, DACO: 4.2.1

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